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PROGNOSIS OF SUBARACHNOID HAEMORRHAGE

A STUDY OF 120 PATIENTS WITH UNOPERATED INTRACRANIAL RTERIAL ANEURYSMS AND 267 PATIENTS WITHOUT VASCULAI LESIONS DEMONSTRABLE IN BILATERAL CAROTID ANGIOGRAMS

BY

MIRJA TAPPURA

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SUPPLEMENTUM 392

FROM THE NEUROSURGICAL CLINIC, HELSINKI UNIVERSITY CENTRAL HOSPITAL
HEAD PROFESSOR E. E. KALLIO, M.D.
NEUROSURGEON-IN-CHIEF G. AF BJÖRKESTEN, M.D.

PROGNOSIS OF SUBARACHNOID HAEMORRHAGE

A STUDY OF 1 0 PATIENTS WITH UNOPERATED INTRACRANIAL ARTERIAL ANEURYSMS AND 26 PATIENTS WITHOUT VASCULAR LESIONS DEMONSTRABLE IN BILATERAL CAROTID ANGIOGRAMS

(WITH 21 TABLES AND 5 FIGURES)

BY

MIRJA TAPPURA

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Helsinki, November 1962

Mirja Tappura

CONTENTS

1 INTRODUCTION AND PROBLEMS OF PRESENT INVESTIGATION

The term subarachnoid haemorrhage means bleeding into the subarachnoid space, accompanied by symptoms and signs of increased intracranial pressure and meningeal irritation. Subarachnoid haemorrhage is always a symptomatic diagnosis, it is not a disease entity

The earlier investigations of the prognosis of subarachnoid haemorrhage showed a mortality that, although high on the average, varied within rather wide limits. There are numerous reasons for these conflicting results. Some of the investigations were made in hospitals that mainly admit patients whose case is acute; some series were collected from neurological and neurosurgical clinics, with their considerable waiting lists. The most severely affected patients die within a few hours and never reach the hospital, those with the mildest symptoms never seek for treatment. The statistics obtained from autopsy series are also different from those of patients surviving their first attack of subarachnoid bleeding. An accurate analysis of the cases is very important, most of the published statistics are by no means comparable and adding together the figures from different publications and drawing conclusions from them may also lead to incorrect results.

The etiology of subarachnoid haemorrhage has been the object of numerous investigations over a period of more than a hundred years. The rôle of ruptured intracranial aneurysms in the etiology of subarachnoid haemorrhage was early recognized, and up to Jan. 1937 accounts of 1125 cases of intracranial aneurysm had been published in all (McDONALD & KORB 1939). Since then a voluminous literature has elucidated various sides of the problem. On the basis of previous investigations and his own series, WALTON (1956) stated that a ruptured intracranial arterial aneurysm was the cause of subarachnoid haemorrhage in about 80 per cent, and an arteriovenous malformation in 10 per cent of cases; the remaining 10 per cent were made up partly of cases where the bleeding was caused by various uncommon diseases (blood dyscrasias, thrombosis, inflammatory conditions, etc.), and partly of cases where it was impossible to discover the source of bleeding with the present means of investigation. WALTON also stated that in a few cases the subarachnoid haemorrhage was an extension of primary cerebral haemorrhage of hypertensive or atherosclerotic origin.

Before cerebral angiography was introduced by EGAS MONIZ in 1927 it was for

There are only a few follow-up studies concerning the prognosis of conservativ ely treated patients with verified intracranial arterial aneurysms. An active surgical treatment for these aneurysms has been generally accepted and a conservative treatment has been reserved for only a few groups. Operation has been withheld because of old age complicating medical illnesses, reaction to carotid compression aneurysms considered inoperable the presence of multiple aneurysms, recency of bleeding, and because some of the patients refused surgical treatment.

The mortality of conservatively treated patients with erified aneurysm is reported by the following authors; in most series the aneurysm was demonstrated angiographically on operation, or at the autopsy

As mentioned above Odom *et al.* (1952 a) reported a mortality of 90 per cent. It is apparent that the diagnosis of these aneurysms was mostly made at th autopsy which explains the very high mortality in their series.

Kristiansen (1956) published an ac count I a series of 58 patients with aneurysm 35 patient (60 per cent) died. He did not evaluate the long term mor tality rate due to recurrence of bleeding.

McKissock & W lsh (1956) reported 108 medically treated patients with aneurysm the t tal mortality being 51 per cent. In their f rther series of 1 0 conservativ ly treated patient with aneurysm M Kissock *et al* (1960 a) reported mortal ty f 47 per cent.

Benson (1958) analyzed 20 verified aneurysm cases which were treated conservativ ly or died before planned surgery 7 died from recurrence of haemorrhage 2 died of another disease, and 3 were unreported. Benson considered that conservatively treated aneurysm patients that survived the dangerous early period had a relatively favourable prognosis.

In their series Drake & Jory (1960) had 40 patients who were known to have bled from an aneurysm and had not been operated upon. 21 patients died the mortality percentage thus being 52.5.

The only publication where aneurysm cases for conservative treatment were chosen at random is the investigation made by McKissock *et al* (1960 b). They included in the trial two groups of patients with aneurysm on the internal carotid — posterior communicating junc tion 48 patients were treated conservati ely 46 were operated upon, and both groups were followed up The total number of deaths in the conservatively treated group was 20 (42 per cent).

This short survey of the literature shows that there seems to be a marked prognostic difference between subarachnoid haemorrhage patients with demonstrated but conservatively treated intra cranial arterial aneurysms and patients with normal angiographic findings. The series published hitherto are comparati ely small, and there are only few reports directly comparing these two groups t each other In addition, there are several factors (age sex, hypertension, symptoms and signs in connection with the bleeding, *inter alia*) whose rôle in the prognosis has not yet been satisfactorily clarified.

Without exact knowledge of the natural course of a disease it is difficult or even impossible to judge how great a

the most part impossible to find out *in vivo* the etiological factor behind a subarachnoid haemorrhage Before angiography was more widely acknowledged and the first technical difficulties overcome, the only way to make a sure diagnosis of the underlying cause was autopsy or very rarely operation. It is only in the last 15—20 years that the modern development of x-ray technique (better contrast media, different oblique exposures, systematically performed bilateral carotid and vertebral angiographies, and serial angiographic investigations) has made the diagnosis of intracranial vascular lesions increasingly exact. But even *now the x-ray technique is not perfect* Arterial aneurysms or small arteriovenous malformations are not always *detectable. a small aneurysm may hide* behind a larger vessel or it may have thrombosed after the first bleeding and minute arteriovenous *malformations may* not fill in the angiogram or they may have been destroyed by the bleeding

ODOM *et al* (1952 *a*) *seem to have been* the first to point out that the mortality was different in subarachnoid haemorrhage *patients with verified intracranial* aneurysms and patients in whom no vascular lesions could be demonstrated They grouped their 318 patients with subarachnoid haemorrhage into five categories according to the etiology and found that in the group of *patients with* conservatively treated intracranial aneurysms the mortality was 90 per cent whereas it was 24 *per cent in the group* where no cause for the bleeding could be demonstrated

Later several *investigators came to the* same conclusions as ODOM *et al* in comparing the prognosis of patients with proven aneurysms *and patients without* demonstrable vascular lesions.

None of PARKINSON's (1955) 22 patients with *subarachnoid haemorrhage* without proven aneurysm died. The mortality in recurrent bleeding in 8 cases of *saccular aneurysm treated conservatively* was 87 per cent (7 out of 8) PARKINSON's numbers were small, but he *pointed out the fallacy of drawing prognostic* conclusions from any figures if cases of subarachnoid haemorrhage were *grouped collectively*

AF BJÖRKESTEN & TROUPP (1957) also compared the prognosis for subarachnoid *haemorrhage patients having arterial* aneurysm with that for patients having normal bilateral carotid angiograms. The *mortality in the aneurysm group was 55* per cent (22 out of 40) and in the no aneurysm group 5 per cent (3 out of 61). AF *BJÖRKESTEN & TROUPP pointed out that* it was essential to differentiate between cases with aneurysm and cases in which *the angiographic findings were normal.*

BENSON (1958) also stressed a point about comparing a conservatively treated *group of subarachnoid haemorrhage* patients with a surgically treated group the groups were actually incomparable *because the first one* included a considerable number of cases where the etiology of the bleeding was unknown

The mortality of patients with subarachnoid haemorrhage but without demonstrable vascular lesions was reported by DUNSMORE & POLCYN (1956) to be 25 per cent by WALSH (1956) 12 per cent by HÖÖK (1958 b) 5 8 per cent, *by LEVY* (1960) 13 per cent, and by DRAKE & JORY (1960) 22 per cent.

There are only a few follow-up studies concerning the prognosis of conservatively treated patients with verified intracranial arterial aneurysms. An active surgical treatment for these aneurysms has been generally accepted and a conservative treatment has been reserved for only a few groups. Operation has been withheld because of old age, complicating medical illnesses, reaction to carotid compression, aneurysms considered inoperable the presence of multiple aneurysms, recency of bleeding, and because some of the patients refused surgical treatment.

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II EARLIER INVESTIGATIONS

A HISTORICAL SURVEY OF THE LITERATURE

According to WALTON (1956) early medical writers, HIPPOCRATES, CELSUS and AVICENNA, were familiar with the syndrome generally called apoplexy. CELSUS was the first to describe a middle meningeal haemorrhage. AVICENNA also recognized that apoplexy was often due to a sanguineous humour effused suddenly about the ventricles. It was not until the middle of the 17th century that WEPFER clearly realized the relationship between intracranial haemorrhage and apoplexy. BRUNNER reported on the importance of aneurysms on the small cerebral vessels in connection with cerebral haemorrhage. Nevertheless, none of these authors reported any certain cases of subarachnoid haemorrhage. DIONIS (1718) was the first to describe two fatal cases in which the cerebral ventricles were distended by blood, but he did not give any details of the site of origin of the haemorrhage.

MORGAGNI (1761) did not separate subarachnoid haemorrhage from other forms of apoplexy but he definitely described such cases. He considered the ruptured aneurysm to be an important cause of cerebral haemorrhage. He did not personally observe such cases, but he reported one case with unruptured bilateral aneurysms on the posterior communicating artery. It was not until 1778 that BIUMI reported a clear case of subarachnoid haemorrhage caused by a ruptured intracranial aneurysm.

The next significant contribution was made by GULL 1859. In his article he reviewed the literature and reported 6 cases with clinical and post mortem observations; he stated that blood on the surface of the brain in young persons was most probably caused by rupture of an aneurysm.

After GULL's article the literature concerning subarachnoid haemorrhage and intracranial aneurysms increased constantly, numerous new cases and reviews of already published ones being reported. As mentioned before MCDONALD & KORB (1939) collected 1125 cases published before Jan. 1937 and 314 of these were published before 1900. Despite these numerous reports, the general picture of subarachnoid haemorrhage and intracranial aneurysms remained confused for many years. French authors (GINTRAC 1869, HAYEM 1872, FROIN 1904) did not accept the view that subarachnoid haemorrhage was caused by rupture of an aneurysm and they seemed to consider other causes, like bacterial infections, cerebral haemorrhage, arteriosclerosis, diseases of the blood, sagittal

surgical risk should be taken in a given case in order to give the patient a better chance for survival without complications than he would have with conservative treatment.

The aim of the present investigation is to find an answer to the following questions.

1 How does the prognosis of subarachnoid haemorrhage patients with unoperated verified intracranial arterial aneurysms compare with that of patients with normal bilateral carotid angiograms, most of the patients in both groups having survived their first subarachnoid bleeding?

a What is the incidence interval and mortality of recurrences of haemorrhage?

b What is the morbidity caused by subarachnoid haemorrhage?

2. Which factors affect the prognosis?

a age and sex.

b concomitant diseases.

c. symptoms and signs connected with the haemorrhage.

d. size and location of the aneurysm.

it was diagnosed more frequently. Subarachnoid haemorrhage was reported by MARTLAND (1939) to cause 2 per cent of the sudden deaths that occur. HELPERN & RABSON (1950) surveyed 2030 autopsied cases of sudden death and found that 4.7 per cent were due to subarachnoid haemorrhage. Statistics given by the English Registrar-General (WOLFF 1933) showed that in England and Wales there were 1316 deaths in 1949 and 1676 deaths in 1950 due to subarachnoid haemorrhage. Taking into account the survivors, WALTON (1956) presumed that about 3000 cases occurred annually in this population. KRISTIANSEN (1936) estimated the occurrence as 3 cases per 50000 people in one year.

A comparison between subarachnoid haemorrhage and other cerebrovascular diseases was made by STEVENSON (1936). He reported that subarachnoid haemorrhage formed 7 per cent of all cases of cerebrovascular diseases and felt that subarachnoid haemorrhage was almost as common as intracerebral haemorrhage. Other authors (OHLER & HURWITZ 1932, RICHARDSON & HYLAND 1941, ASK-UPMARK & INGVAR 1950, MERRITT 1955) reported that cerebral haemorrhage was more common than subarachnoid haemorrhage. ROWBOTHAM & HAY (1935) reported the incidence of subarachnoid haemorrhage as 2.3 per cent of all cerebrovascular diseases. Comparison of subarachnoid haemorrhage and intracerebral bleeding in this way seems unjustifiable, because it is impossible to differentiate between intracerebral haemorrhage with or without localizing signs and bloody spinal fluid on the one hand and pure subarachnoid haemorrhage with no intracerebral component on the other (LEVY 1960).

The incidence of intracranial aneurysms is mainly reported on the basis of autopsies. It has been estimated that intracranial arterial aneurysms are discovered in 0.25 per cent (PITT 1890), 0.81 per cent (FEARNSIDES 1916), 0.69 per cent (CONWAY 1920), 0.5 per cent (SCHMIDT 1930), 0.87 per cent (RICHARDSON & HYLAND 1941), and 1.1 per cent (MITCHELL & ANGRIST 1943) of autopsies. STEHBENS (1954) reported an incidence of 3.7 per cent and WALTON (1956) of 0.93 per cent in brain autopsies. HOUSEPIAN & POOL (1958) reported that the population incidence of intracranial aneurysms, the figure being based on the number of adult brains examined, was consistently 0.5 per cent from 1914—1930. Since 1931 this figure has increased to 2.1 per cent, apparently due to a larger number of brain examinations. The overall incidence was 1.3 per cent if children were included. When the calculation was made on the basis of the total number of autopsies, including those in which no brain examination was performed, the figure dropped to 0.8 per cent. When the incidence of symptomatic aneurysm cases was calculated on the basis of the total number of brains examined, 0.2 per cent resulted.

2. ETIOLOGY

The etiology of subarachnoid haemorrhage is widely discussed in the literature. In the oldest investigations the etiology remained obscure, especially in the surviving patients, because the methods of investigation were not adequate. Before the introduction of angiography the

sinus thrombosis, eclampsia sunstroke tumour or cyst, and syphilis of equal importance. As late as 1923 GOLDFLAM considered that the bleeding was caused by capillary oozing due to vasomotor instability

In the Anglo-Saxon countries the literature concerning intracranial aneurysms increased constantly In particular FEARNSIDES (1916) and TURNBULL (1915 1918) greatly helped to elucidate the problem. In his publications, SYMONDS (1923 1924) tried to correlate the findings of the previous writers. He reviewed 124 cases from the literature and 5 cases of his own and concluded that ruptured intracranial aneurysm was the most important cause of subarachnoid haemorrhage but he agreed that other factors may play a part, too

SYMONDS's opinions were generally accepted although SANDS (1929) SHELBURNE (1937) FETTER (1943) and VORIS (1949) among others, continued to present sunstroke and various other conditions as important in the etiology of subarachnoid haemorrhage On the other hand, many authors suggested that subarachnoid haemorrhage was always the result of ruptured intracranial aneurysm (AYER 1934 and others)

SYMONDS's correct conclusions are valid even now but it is agreed that other pathological conditions, and in particular arteriovenous malformations, may produce an identical clinical picture (OLIVECRONA & RIIVES 1948 NORLEN 1949 MARTIN 1951 MACKENZIE 1953 KRENCHEL 1961)

In the last 30 years a voluminous literature has been published elucidating various sides of subarachnoid haemorrhage and intracranial arterial aneurysm (STRAUSS et al 1932, NATTRASS 1933 TAYLOR & WHITFIELD 1936 RICHARDSON & HYLAND 1941 SAHS & KEIL 1943 DANDY 1944 HAMBY 1948, 1952, WALTON 1956 and others) Follow-up studies of survivors have been made, for example by RICHARDSON & HYLAND (1941) MAGEE (1943) WOLF et al (1945) HAMBY (1948 1952) HYLAND (1950) ASK UPMARK & INGVAR (1950) WALTON (1956) and others.

The development of vascular surgery of the cranial vessels has made the treatment of intracranial aneurysms mainly a surgical problem After DANDY's (1944) pioneer work, numerous surgeons contributed to the technical development of aneurysm surgery However it falls outside the scope of this survey to go into further details of the literature concerning this problem

B. INCIDENCE AND ETIOLOGY OF SUBARACHNOID HAEMORRHAGE

1 INCIDENCE

There seems little point in assessing the incidence of subarachnoid haemorrhage in the general population, because it is not a definite disease however the incidence is reported in many publications.

According to TAYLOR & WHITFIELD (1936) the incidence of subarachnoid haemorrhage was 0 63 per thousand admissions in a general hospital WALTON (1956) reported the incidence as 1 7 per thousand admissions in a similar hospital and suggested that either the condition occurred more often in recent years, or

it was diagnosed more frequently Subarachnoid haemorrhage was reported by MARTLAND (1939) to cause 2 per cent of the sudden deaths that occur HELPERN & RABSON (1950) surveyed 2030 autopsied cases of sudden death and found that 4.7 per cent were due to subarachnoid haemorrhage. Statistics given by the English Registrar-General (WOLFE 1953) showed that in England and Wales there were 1316 deaths in 1949 and 1676 deaths in 1950 due to subarachnoid haemorrhage Taking into account the survivors, WALTON (1956) presumed that about 3000 cases occurred annually in this population. KRISTIANSEN (1950) estimated the occurrence as 3 cases per 50000 people in one year

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2. ETIOLOGY

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underlying cause of subarachnoid haemorrhage could be revealed with certainty only on autopsy but very few patients were given thorough post mortem examination

Most authors tried to divide the cases with subarachnoid haemorrhage into two groups. One group was termed »spontaneous subarachnoid haemorrhage« a designation suggested by GOWERS (1888) and SYMONDS (1924) in order to exclude subarachnoid haemorrhage caused by external trauma Those with traumatic lesions formed another group of patients, this group also included those with neonatal haemorrhages, which were mostly considered to be due to birth injury On the other hand SAHS & KEIL (1943) suggested that the term »spontaneous subarachnoid haemorrhage« should be discarded because it was meaningless and confusing and because in the majority of cases a cause for the bleeding could be demonstrated ruptured intracranial aneurysm extension of a massive intracerebral haemorrhage into the subarachnoid space haemorrhage from a neoplasm meningeal inflammation or blood dyscrasia On the whole the division of the patients into »spontaneous« and other groups seems to have remained inconsistent and confusing until recent years

Early writers (GULL 1859 EPPINGER 1887 SYMONDS 1923 1924 and others) were fully aware of the fact that a ruptured intracranial aneurysm was an important and frequent cause underlying subarachnoid haemorrhage AYER (1934) suggested that the terms »spontaneous subarachnoid haemorrhage« and »ruptured intracranial aneurysm« were actually synonymous. On the other hand, STRAUSS & TARACHOW (1937) felt that intracranial aneurysms were of minor importance and other conditions, particularly hypertension and arteriosclerosis were the cause of bleeding in the majority of cases. The same opinion was put forward by NATHANSON et al (1953)

The etiological factors vary in different publications depending mainly on the thoroughness of the investigation and the quality of the angiographic technique. Up to now there are no investigations where all the patients with subarachnoid haemorrhage have been subjected to complete angiographic investigation and autopsies have not been performed in more than a fraction of the cases that died The following figures are reported concerning the frequency of intracranial aneurysms as the etiological factor in subarachnoid haemorrhage

ASK UPMARK & INGVAR (1950) found 28 aneurysms in 17 post mortem examinations, their total series consisted of 138 cases.

In his series of 130 patients with subarachnoid haemorrhage HAMBY (1948, 1952) found 41 aneurysms. The cause was able to be determined with certainty in 6 operations and 41 autopsies. He assumed that in the unproved cases the aneurysm frequency would probably be the same HYLAND (1950) reported that in his series of 191 cases with subarachnoid haemorrhage 44 aneurysms were found in 55 autopsies. DEKABAN & McEACHERN (1952) showed that 30 of their 100 cases with subarachnoid haemorrhage had an aneurysm In ODOM's et al. (1952 a) series the corresponding figures were 102 and 316 In a series of

422 cases of subarachnoid haemorrhage reported by TIMBERLAKE & KUBIK (1952) 280 patients had or were thought to have an intracranial aneurysm. This number is certainly not very accurate because only 31 patients had angiograms, and 68 were autopsied. WOLFE (1953) had 93 patients with subarachnoid haemorrhage: autopsy was performed on 44 and a ruptured aneurysm was found in 33 of these and in 2 survivors. In 1951 FALCONER found aneurysms in 100 of his 148 cases. JACOBSON (1951) surveyed several series from the literature and stated on the basis of these that the frequency of aneurysms as the cause of subarachnoid haemorrhage was 38.6 per cent. KRISTIANSEN (1955) found aneurysms in 58 out of 130 cases of subarachnoid haemorrhage, WALTON in 63 out of 312. In WALTON's series 69 cases were autopsied and 10 had an angiography performed, thus a great number were not thoroughly investigated.

In recent studies, combining information obtained from frequent angiographic investigation with that discovered on operation or autopsy, more adequate and reliable knowledge of the incidence of intracranial vascular lesions causing subarachnoid haemorrhage is to be found. As mentioned previously it is estimated by WALTON (1956) that intracranial ruptured aneurysms are the cause of subarachnoid bleeding in 60 per cent of cases, arteriovenous malformations in 10 per cent, the remaining 10 per cent are made up of patients in whom the cause of bleeding either is uncommon or cannot be demonstrated at all. According to many authors, however, the group where no cause is found is considerably larger, 20—36 per cent (FALCONER 1958, KRAYENBÜHL & YASARGIL 1958, MCKISSOCK *et al.* 1958, HAMBLIN 1961).

Intracranial haemorrhage either in the form of intracerebral haematoma or of subarachnoid haemorrhage, is, together with epilepsy, the most frequent sign of *an arteriovenous malformation* and occurs in about half of the patients in most series (OLIVECRONA & RIIVES 1948, PATERSON & MCKISSOCK 1956, OLIVECRONA & LADENHEIM 1957, TÖNNIS 1957, KRENCHEL 1961). Subarachnoid haemorrhage was present in 39 of 125 cases in the series of OLIVECRONA & LADENHEIM and in 42 out of 150 cases in KRENCHEL's series. Many authors (CRAWFORD & RUSSELL 1956, HYLAND 1961) have emphasized that the haemorrhage may be caused by a minute cerebral arteriovenous malformation, which may be so completely destroyed by the bleeding that it is later extremely difficult to find if not specially and carefully looked for at the autopsy.

The changes in the arterial wall caused by *arteriosclerosis and/or hypertension* and the mechanical pressure factor accompanying high blood pressure have aroused much interest in considering the etiology of subarachnoid haemorrhage. Several investigators have tried to correlate hypertension with subarachnoid haemorrhage on the one hand and with the development and rupture of aneurysms on the other. SYMONDS (1921) was already of the opinion that arterial degeneration of the type generally known as arteriosclerosis, associated with cardiac or renal disease, may lead to direct rupture of the artery or to the formation of an aneurysm with subsequent rupture.



He had 29 arteriosclerotics among 124 patients with subarachnoid haemorrhage. ODOM *et al* (1952 a) reported that 43 out of their 316 cases had a hypertensive cardiovascular *disease as the cause of the* subarachnoid haemorrhage. NATHANSON *et al.* (1953) also had the impression that hypertension arteriosclerosis was a very important factor in causing subarachnoid haemorrhage in many cases in the form of an extension of an originally intra cerebral bleeding

McDONALD & KORB (1939) reported that in 67.3 per cent of 572 cases pathological changes were found in the arteries in the majority of the cases (283 patients) *the changes* were *sclerotic The incidence* of arteriosclerosis was remarkably *high in young people About 70 per cent* of the patients in the series of RICHARDSON & HYLAND (1941) had atheromatous changes in the arteries DANDY (1944) too, noted the presence of arteriosclerosis in aneurysm patients. Also WALKER & ALLEGRE (1954) reported the incidence of atherosclerosis to be twice as high in arteries of patients with aneurysm as in those from the control series. BAKER & IANNONE (1961) also stressed the point that atherosclerosis might be present as early as in the second decade of life and rapidly increased in frequency after the third decade.

In recent years it has become obvious that even among cases where complete *angiographic investigations* with all possible technical methods are performed there is always a section of *patients in whom no cause for the subarachnoid haemorrhage can be found*

KRAYENBÜHL & YASARGIL (1958) reported that no cause for the bleeding had been found in 155 of 431 cases of subarachnoid haemorrhage *examined by* angiography McKISSOCK *et al* (1958) reported the failure of angiography to *demonstrate a lesion in 31* per cent of cases (140 out of 455) LEVY (1960) reported that for 76 out of 164 cases with subarachnoid haemorrhage no cause could be found in the angiographic investigation

V HOFMANN (1894) EHRENBERG (1936) LUTT (1938) and RICHARDSON & HYLAND (1941) had already suggested that subarachnoid bleeding might come from a very small aneurysm that had escaped detection RIGGS & RUPP (1942) *found 131 small aneurysms (less than* 5 mm in diameter) in 1335 brain exam*inations.* HASSLER *(1961) found minute* aneurysms (less than 2 mm maximum diameter) to be very common. In the microdissection of large cerebral arteries he found 32 minute aneurysms in 27 individuals among 144 preparations from persons of 31 years or more. He described two minute aneurysms that probably caused subarachnoid haemorrhage one had been discovered on operation the other one was found at the necropsy

RUSSELL (1954) stressed that media *defects, which are commonly* considered to be the main cause of the development *of aneurysms* (FORBUS 1930 and others) might sometimes undergo rupture without an actual detectable aneurysm being formed beforehand.

MARGOLIS *et al* (1951) CRAWFORD & RUSSELL (1956), HYLAND *(1961)* and KRENCHEL (1961) considered that minute arteriovenous *malformations, not filling* in the angiograms and difficult to find

at the autopsy might be the cause of the bleeding in a considerable number of cases of subarachnoid haemorrhage of obscure origin.

The literature reviewed above justifies the presumption that a notable part may be played by minute aneurysms and small arteriovenous malformations in the etiology of the bleedings in the subarachnoid space: these vascular anomalies may thrombose after bleeding and thus be no longer detectable in the angiographic investigations. They may also be extremely difficult to find at the autopsy if not specially looked for.

In the etiology of subarachnoid haemorrhage there are numerous *other factors* reported by several authors. WALTON (1956) listed a considerable number of them, some of them being extremely rare.

Recently GROCH *et al.* (1960) and SILVERSTEIN (1961) reviewed the correlation between different blood diseases and intracranial haemorrhage. GROCH *et al.* reported 93 cases with leukemia, in 49 per cent of these there was intracranial haemorrhage, mostly in the white matter of the hemispheres. SILVERSTEIN had 58 patients in whom a bleeding tendency due to a blood disease caused an intracranial haemorrhage. The bleeding mostly occurred in the brain tissue: there were only 9 subarachnoid haemorrhages, but out of 43 intracerebral haematomas 15 extended to the subarachnoid space.



III PRESENT SERIES PRINCIPLES OF SELECTION AND FOLLOW UP

During the years 1938—1959 inclusive intracranial arterial aneurysms were diagnosed in 471 patients in the Neurosurgical Department of the Finnish Red Cross Hospital later named the Neurosurgical Clinic of the Helsinki University Central Hospital During the same period the number of patients having verified subarachnoid haemorrhage with no discovered cause for the bleeding was 397 This figure also includes incompletely invesgatedti patients. Arteriovenous malformations were diagnosed in 72 patients.

For the present investigation two groups of patients were selected. The first group consisted of 120 patients In all these patients arterial aneurysms, one or multiple, were found in the cerebral angiograms, at the autopsy or during exploratory operation but the patients were not subjected to surgical therapy This group formed the »*aneurysm series*» All of the patients had had one or more attacks of subarachnoid bleeding except for 9 patients who had ophthalmoplegia without a verified subarachnoid haemor rhage.

The second group consisted of 267 patients with at least one attack of verified subarachnoid bleeding and normal bilateral carotid angiograms. 32 of the no aneurysm cases also had unilateral vertebral angiography performed These patients formed the »*no aneurysm series*» This series mainly comprised patients admitted after the year 1947 because before that time bilateral carotid angiography was only rarely performed in this clinic.

All of the patients included in this investigation were sent letters inquiring about their present state of health a smaller section of the patients were examined in the hospital. Inquiries were also sent to hospitals where the patients had been treated after their discharge from this clinic. If the patient was reported to have died the death certificate was obtained and autopsy reports were studied whenever possible

All the 387 patients were traced some of them abroad one in prison and two in a mental asylum

All the inquiries were sent during the summer months of 1961 and the follow up was completed before the end of that year Thus, all the survivors had a follow up period of at least one and a half years, the longest being 23 years (Table 1) The mean follow-up period in the aneurysm series was 5 years for the survivors and 2 years for patients who died due to the subarachnoid haemorrhage. The corresponding figures in the no aneurysm

TABLE 1

Length of follow-up period

		Length of follow-up period in years																Total
		1½	2	3	4	5	6	7	8	9	10	11	12	13	14	21	23	
ANEURYSM SERIES	Surviving patients	1	21	12	9	4	1	1	3	1	2	—	1	2	1	—	1	60
	Deaths from other diseases	—	1	2	—	1	1	1	1	—	—	—	—	—	—	—	—	7
	Total	1	22	14	9	5	2	2	4	1	2	—	1	2	1	—	1	67
NO ANEURYSM SERIES	Surviving patients	—	[illegible]	47	45	33	31	17	16	7	2	—	—	1	—	1	—	250
	Deaths from other diseases	2	—	—	2	3	—	—	1	—	—	—	—	—	—	—	—	8
	Total	2	[illegible]	47	47	36	31	17	17	7	2	—	—	1	—	1	—	258

series were 4.2 years and 1½ years. The patients who died of an unrelated disease were included in the group of survivors.

The follow-up period was counted from the first subarachnoid bleeding of the patient, or from the sudden onset of an ophthalmoplegia without verified bleeding, and not from the hospital admission, which varied considerably in relation to the time of the haemorrhage. In most cases the first bleeding was a verified one, however in some cases with recurrent bleeding the follow-up period was counted from a clinically typical, but unverified first haemorrhage.

The length of the follow-up period for the survivors and for the patients who died from unrelated diseases appear from Table 1; the corresponding period for the patients who died from recurrence of haemorrhage is shown in Tables 3—6. The figures in the week and month columns indicate periods within which recurrences occurred. After 1½ years every figure in the year column indicates a mean; for example, the figure 2 represents a period extending from 1½ to 2½ years; the figure 3 represents a period from 2½ to 3½ years; and so on.

All the angiograms were re-examined in co-operation with neurosurgeons or neuroradiologists. In a few cases the x-ray films could not be found, and the previously written report of the radiologist had to be considered sufficient. In all patients with bilateral carotid angiography the filling of the posterior cerebral arteries was carefully noted. It may be of interest to note that in the re-examination of the films of the no aneurysm series one certain intracranial arterial aneurysm and two intracranial tumours were revealed; the tumour cases were excluded from the present series.

It must be stressed that this clinic is the only neurosurgical centre in the country and admits patients after a considerable waiting period; thus the series is highly selected, consisting mainly of patients who have survived at least one attack of subarachnoid bleeding.

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ature by anyone but Odom *et al.* (1952a), who gave a mortality percentage of 16, the total number of patients being 143

In the present series the first attack of subarachnoid bleeding was considered to be the first verified subarachnoid bleeding, or the first clinically typical unverified bleeding in the patient's history or the sudden onset of ophthalmoplegia accompanied by retrobulbar or general headache.

In the aneurysm series there were 57 patients with only one subarachnoid haemorrhage 5 of these died from this bleeding or its sequelae. The interval between the attack and death was 1 day 3 days, 4 days, 4 weeks and 3 months, respectively

In the no aneurysm series the number of patients who suffered only one subarachnoid haemorrhage was 222; only one patient died, slowly deteriorating in 6 months.

It should be stressed again that this *series is highly selected thus, these figures* are not descriptive considering the problem as a whole

2. INCIDENCE, INTERVAL AND MORTALITY OF RECURRENT HAEMORRHAGE

Even if the clinical picture of a subarachnoid haemorrhage is typical in general the diagnosis of recurrent bleeding may sometimes be difficult to establish except through lumbar puncture or at the autopsy It is possible that in some cases an impairment in the clinical course of the illness, following a single haemorrhage has been erroneously interpreted as due to a recurrent haemorrhage Some authors (Larsen & Vangaard 1941 Richardson & Hyland 1941) have regarded all recurrences of bleeding after a short interval as exacerbations of the primary haemorrhage Larsen & Vangaard only regarded a bleeding from a *new starting point* as a recurrence. Walton (1956) and others considered relapses, following a period of clear improvement in the clinical status, to be true attacks of recurrent bleeding

In Magee's series (1943) a recurrent haemorrhage occurred in 50 of the total of 150 patients (33 per cent). The highest incidence of the second attack fell in the first month with a peak in the third week, 32 of these 50 patients died from the recurrent bleeding (21 per cent of the total) Wolf *et al.* (1943) followed up 46 cases with subarachnoid haemorrhage These patients had recurrences in 52 per cent of cases and 22 per cent of the total number died from recurrent haemorrhage In Hamby's (1948, 1952) series of 130 patients recurrences occurred in 35.4 per cent of cases, and 28.5 per cent of the total died. Hamby stated that when a patient had a second attack of subarachnoid bleeding his chances of dying rather than living were increased to about two to one almost a complete reversal of the case for patients having single attacks. Hyland (1950) followed up the patients in the original series of Richardson & Hyland (1941) and added cases admitted since the last publication, the total number of the patients thus being 191 After discharge from the hospital 14 died *from recurrence* but he was able to trace *only* 67 out of 91 patients who survived. All the 11 patients *died* within the first three months after discharge

IV PRESENT SERIES COMPARED TO EARLIER INVESTIGATIONS

A. COURSE OF ILLNESS

1 MORTALITY IN FIRST ATTACK

The mortality figures for subarachnoid haemorrhage are formed from two groups of patients, those who die from their first attack of subarachnoid bleeding and those who survive the first attack but succumb in one of the following attacks. Many patients in the first group die suddenly never reaching the hospital, and only a few are autopsied Thus mortality figures calculated on the basis of hospital patients are fallacious, as they *show a mortality lower than the reality* Also insufficient information about possible *haemorrhages in the patients previous* history affects the reliability of the figures.

In non-differentiated groups of patients with subarachnoid haemorrhage the mortality figures for the first bleeding vary within rather wide limits. MAGEE (1943) reported that 52 out of 150 patients (34 per cent) died from the first attack. The corresponding figures according to other authors were. WOLF *et al.* (1943) 5 out of 46 (10 per cent) HAMBY (1948, 1952) 44 out of 130 (34 per cent) ASK UPMARK & INGVAR (1950) 38 out of 138 (27 per cent), HYLAND (1950) 74 out of 191 (39 per cent) JACOBSON (1954) 28 per cent, WALTON (1956) 91 out of 312 (29 per cent) ROWLEY *et al* (1957) 74 out of 157 (48 per cent)

The mortality in the first attack of bleeding for patients with a verified intracranial arterial aneurysm was estimated to be 45 per cent by HAMBY (1952). ODOM *et al* (1952 a) reported that 35 per cent out of 52 conservatively treated aneurysm patients died from the first bleeding FALCONER (1958) reported a mortality of 30 per cent. BENSON (1958) reported that 9 patients out of 40 aneurysm patients (22 per cent) died from the first attack or from its sequelae HOUSEPIAN & POOL (1958) reported that out of 113 autopsy cases with intracranial arterial aneurysms, 50 per cent succumbed in their initial attack. The term »*initial attack*» *was applied to those cases* which had a single attack or repeated *bleeding without significant remission* or symptom-free interval prior to the terminal episode. In their report on a controlled trial of the conservative and the surgical treatment of »posterior communicating» aneurysms MCKISSOCK *et al* (1960 b) described 36 cases which were admitted because of their first subarachnoid haemorrhage; 2 out of these 36 died due to the bleeding This extremely low mortality must be without doubt influenced by the natural selection of the patients.

The mortality rate in the first attack of haemorrhage for patients *with subarachnoid* haemorrhage *without* any known cause is not reported *in the liter*

(80 per cent) The time of occurrence of the third haemorrhage showed a similar pattern in relation to the second, with the maximum incidence in the first and second week. 29 out of 155 cases with a second bleeding died. This did not include patients who were subjected to operation. Of 155 cases with recurrent bleeding 113 had two attacks, 31 three, and 8 had more than three haemorrhages.

In their later report McKissock *et al.* (1960 a) reported 772 patients with intracranial aneurysm 170 of which were treated conservatively. These researchers ga e the total mortality including all deaths irrespective of cause and time, as 47 per cent (81 out of 170) 74 per cent of all the deaths in the conservatively treated group occurred within 1 month of admission.

In their series of 40 conservati ely treated aneurysms AF Björkesten & Troupp (1957) had a mortality of 55 per cent (22 out of 40) from recurrent haemorrhage 8 patients died within 1 month, within 1—2 months, 5 within 2—6 months, 2 within 6—12 months, 1 in 3—5 years, 1 in 5—10 years.

In their report on 113 autopsy patients with aneurysms Hourepian & Pool (1958) had a total mortality of 71 per cent, and out of these 21 per cent died from recurrent haemorrhage; 27 per cent did not bleed at any time 61 per cent died within 1 weeks, 73 per cent within three months, 83 per cent within one year and 96 per cent within 5 years; the longest survival time was 11 years. Hourepian & Pool stated that if a patient survived the first 3 months after the time of onset f his initial symptoms, he had a progressi ely better chance of living longer

McKissock *et al* (1960 b) admitted 36 patients with posterior communicating aneurysm, all of them after the first haemorrhage; 2 of these died due to this initial attack. 17 out of 31 had a second attack, from which 10 died. Thus the mortality rate was 60 per cent for the second attack and 30 per cent for all patients (10 out of 31). Four out of 7 survivors had a third haemorrhage, giving a mortality of 75 per cent (3 out of 4) for the third bleeding and 45 per cent for all patients at risk (3 out of 7). The total mortality rate from recurrent bleeding was 40 per cent (13 out of 31).

The frequency interval and mortality of recurrent haemorrhage for the group of *patients in whom no cause for the subarachnoid bleeding* was found was reported by the following authors.

Odom *et al.* (1952 a) reported a mortality of 8 per cent from recurrent bleeding in the no cause found group of 143 patients. The total number of recurrences was not reported and the follow-up period was not given

Walsh (1956) reported 93 patients with no known cause for the subarachnoid haemorrhage 6 died in hospital within a short time. Of the 87 patients who were discharged from the hospital 5 died from definite recurrent haemorrhage. The total mortality from recurrence was thus 11 patients out of 93 (12 per cent) The total number of recurrences was not given. The follow-up period was 1—11 years, with an average of a little more than 3 years for the survivors. In 6 out of the 11 dead an aneurysm was found on autopsy and in 3 a large intracerebral haematoma was found, indicating that there might have

Ask Upmark & Ingvar (1950) followed up 100 patients, the follow-up time being 1 year or less in 14 cases, 1—5 years in 27 cases, 5—10 years in 27 cases, and 10—33 years in 32 cases. Recurrences occurred in 39 patients (39 per cent) with 23 fatalities. Most of the recurrences occurred during the first 5 years, but even 20 years after the initial attack a recurrent haemorrhage was reported

French & Blake (1950) made an analysis of 603 reported cases of subarachnoid haemorrhage and found that the frequency of recurrences was highest at the beginning of the second week after the primary haemorrhage. 30 per cent occurred within the first two weeks and 57 per cent within the first three weeks.

Walton (1956) reported clear recurrent bleeding occurring in 60 out of 312 cases 47 (78 per cent) of these patients died Most of these recurrent haemorrhages occurred within 4 weeks only in 7 cases was the interval longer The peak was in the second week (25 cases) On the basis of the literature and his own results Walton concluded that recurrent haemorrhage was most likely to occur in the 2nd or 3rd week

Höök (1958 a) reported the fate of a series of 152 patients collected from medical hospitals (72 cases) and neurological and neurosurgical clinics (80 cases) An early prognosis was computed on the basis of an observation period of 8 weeks after the bleeding that caused the patient s admission to the hospital, and a late prognosis was based on a period exceeding 8 weeks. In both the medical and neurological series the mortality was high during the first 24 hours (12.5 per cent) and during the first week (33 and 31 per cent, respectively) During the following weeks the mortality decreased and after 6 weeks it was comparatively low Altogether 25 patients in these series died after the termination of the early observation period of 8 weeks. Höök stated that the risk in the entire series, taking into consideration recurrent haemorrhage after 8 weeks, was 12.5 per cent. The risk of a fatal recurrence of haemorrhage during an observation period of about 7 years was 20 per cent; this was calculated for the 92 patients who survived the first 8 weeks.

Rowley *et al* (1957) had 83 survivors out of 157 patients, 46 could be traced, the follow up period varying between 3 months and 10 years. Recurrent haemorrhage occurred in 8 patients, with 2 fatalities.

There are only few reports on the incidence, interval and mortality of recurrent haemorrhage in a sizeable series of conservatively treated aneurysms. The following reports are reviewed

Odom *et al* (1952 a) reported 52 cases of untreated arterial aneurysms; 85 per cent of the survivors from the initial attack died from recurrent haemorrhage. 31 per cent of the deaths occurred within one week after the haemorrhage 50 per cent within 2 weeks, 66 per cent within 3 weeks, 83 per cent within 4 weeks, 89 per cent within 8 weeks, 96 per cent within 12 weeks, and 100 per cent within 10 years.

McKissock & Walsh (1956) reported 249 cases of intracranial aneurysm, 108 of these patients were treated medically 155 had had more than one attack of haemorrhage the second bleeding occurring within 8 weeks in 123 patients

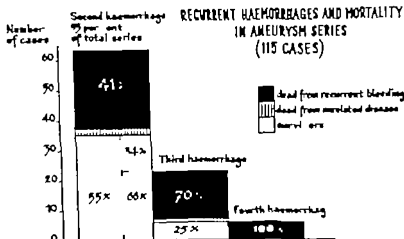


Fig. 1.

TABLE 3

Interval and mortality of first recurrence
63 patients with aneurysm

Location of aneurysm	Number of patients (fatal recurrences)	Weeks 1	2	3	4	5	6	7	8	Months 3	4	5	6	7—12	Years after 1st haemorrhage 1—1½	2	3	4	5	6	7	8	9
Internal carotid	14 (6)	1	2	—	2	1	—	1 (1)	2 (1)	—	—			1 (1)	—	1 (1)	1 (1)	1	—		1 (1)	—	—
Anterior communicating	16 (6)	1	1	3 (1)	—	2	1 (1)	1 (1)	1 (1)	—	1 (1)	—		—	—	—	—	1	1 (1)	1	—	1	1
Middle cerebral	15 (5)	4	3	3 (1)	1 (1)	—	1 (1)	—	—	—	—	—		—	—	—	1 (1)	—	—	—	1	1 (1)	—
Pericallosal	1 (1)	—	—	—	—	—	—	—	—	—	—	—		—	—	1 (1)	—	—	—	—	—	—	—
Posterior cerebral	2 (1)	—	—	—	—	—	1 (1)	—	—	1	—	—		—	—	—	—	—	—	—	—	—	—
Basilar	3 (2)	—	1 (1)	—	—	—	—	—	1 (1)	—	—	—		—	—	1	—	—	—	—	—	—	—
Multiple aneurysms	12 (5)	1	1	1	1 (1)	1	—	—	—	1	—	—	1	—	—	1 (1)	2 (2)	2 (1)	—	—	—	—	—
	63 (30)	39 (13)								5 (2)					19 (11)								

(Number of fatal recurrences in brackets)

been an undiagnosed aneurysm or angioma 2 had subarachnoid haemorrhage the source of which was not found.

Dunsmore & Polcyn (1956) followed up 81 cases of subarachnoid haemorrhage, where no cause was found, 71 patients could be traced 52 surviving patients were followed up for 1—10 years, 18 had been followed up for more than 5 years. There were 18 deaths from recurrent haemorrhage (25 per cent) All the deaths except one occurred within one year after the first attack. Autopsy was performed in 4 cases, and one aneurysm was found In addition to these fatal haemorrhages Dunsmore & Polcyn reported three more recurrences during the follow up period these patients survived

af Björkesten & Troupp (1957) reported recurrences in 18 out of 61 patients in their no aneurysm series, three of them died Two were autopsied and in one an aneurysm was found The shortest follow-up time was 1 year Two of the deaths occurred during the first two months, one in 2—3 years.

Only 18 patients out of the total of 138 of Höök's (1958 b) series were admitted during the first week following the first attack. Two of these (11 per cent) died within the first 8 weeks. After the 8th week there were 9 deaths, 8 from recurrence and one uncertain case. Thus 5.8 per cent died from recurrent haemorrhage The average follow-up period was 4.5 years. In two out of 5 autopsies an aneurysm was found.

Levy (1960) reported 10 deaths from recurrence among his 76 patients with subarachnoid haemorrhage without any known cause Nine of them died within 1 year and 4 months; only one survived 4 years. He considered that if a patient with subarachnoid haemorrhage and a negative angiogram survived 1 year his chances of continued survival were excellent.

In the present aneurysm series the incidence of recurrent haemorrhage and the mortality from recurrence appear from Table 2 and Fig 1 Recurrent bleeding occurred in 63 out of 115 patients who survived the initial haemorrhage (55 per cent) 41 per cent (26 out of 63) died from the second bleeding 2 died of an unrelated disease Of the 35 survivors

TABLE 2

Incidence of recurrent haemorrhage and mortality in recurrence

	Number of survivors after first haemorrhage	Number of patients with recurrence of haemorrhage	Number of deaths from recurrence
ANEURYSM SERIES			
Females	59	29	20
Males	56	34	28
Total	115	63	48
NO ANEURYSM SERIES			
Females	136	25	4
Males	130	20	4
Total	266	45	8

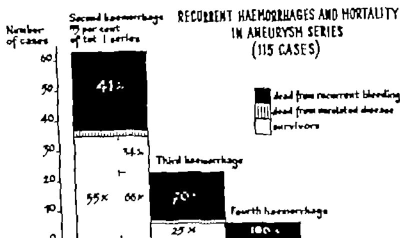


Fig. 1.

TABLE 8

Interval and mortality of first recurrence
63 patients with aneurysms

Location of aneurysm	Number of patients (fatal recurrence)	Weeks 1	2	3	4	5	6	7	8	Months 3	4	5	6	7—12	Years after 1st haemorrhage 1—1½	2	3	4	5	6	7	8	9
Internal carotid	14 (6)	1	2	—	2	1	—	1 (1)	2 (1)	—	—	—	—	1 (1)	—	1 (1)	1 (1)	1	—	—	1 (1)	—	—
Anterior communicating	16 (6)	1	1	2 (1)		2	1 (1)	1 (1)	1 (1)	—	1 (1)	—	—	—	—	—	—	1	1 (1)	1	—	1	1
Middle cerebral	15 (5)	4	3	3 (1)	1 (1)	—	1 (1)	—	—	—	—	—	—	—	—	—	1 (1)	—	—	—	1	1 (1)	
Pericallosal	1 (1)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (1)	—	—	—	—	—	—	—
Posterior cerebral	2 (1)	—	—	—	—	—	1 (1)	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
Basilar	3 (2)	—	1 (1)	—	—	—	—	—	1 (1)	—	—	—	—	—	—	1	—	—	—	—	—	—	—
Multiple aneurysms	12 (5)	1	1	1	1 (1)	1	—	—	—	1	—	—	1	—	—	1 (1)	2 (2)	2 (1)	—	—	—	—	—
	63 (26)	39 (13)								5 (2)					19 (11)								

(Number of fatal recurrences in brackets)

been an undiagnosed aneurysm or angioma 2 had subarachnoid haemorrhage the source of which was not found.

DUNSMORE & POLCYN (1956) followed up 81 cases of subarachnoid haemorrhage, where no cause was found, 71 patients could be traced 52 surviving patients were followed up for 1—10 years; 18 had been followed up for more than 5 years. There were 18 deaths from recurrent haemorrhage (25 per cent) All the deaths except one occurred within one year after the first attack Autopsy was performed in 4 cases, and one aneurysm was found In addition to these fatal haemorrhages DUNSMORE & POLCYN reported three more recurrences during the follow up period these patients survived

AF BJÖRKESTEN & TROUPP (1957) reported recurrences in 18 out of 61 patients in their no aneurysm series, three of them died Two were autopsied and in one an aneurysm was found The shortest follow-up time was 1 year Two of the deaths occurred during the first two months, one in 2—3 years.

Only 18 patients out of the total of 138 of HÖÖK's (1958 b) series were admitted during the first week following the first attack. Two of these (11 per cent) died within the first 8 weeks. After the 8th week there were 9 deaths, 8 from recurrence and one uncertain case. Thus 5.8 per cent died from recurrent haemorrhage The average follow up period was 4.5 years. In two out of 5 autopsies an aneurysm was found.

LEVY (1960) reported 10 deaths from recurrence among his 76 patients with subarachnoid haemorrhage without any known cause. Nine of them died within 1 year and 4 months, only one survived 4 years. He considered that if a patient with subarachnoid haemorrhage and a negative angiogram survived 1 year his chances of continued survival were excellent.

In the present aneurysm series the incidence of recurrent haemorrhage and the mortality from recurrence appear from Table 2 and Fig 1 Recurrent bleeding occurred in 63 out of 115 patients who survived the initial haemorrhage (55 per cent) 41 per cent (26 out of 63) died from the second bleeding; 2 died of an unrelated disease Of the 35 survivors

TABLE 2

Incidence of recurrent haemorrhage and mortality in recurrence

	Number of survivors after first haemorrhage	Number of patient with recurrence of haemorrhage	Number of deaths from recurrence
ANEURYSM SERIES			
Females	59	29	20
Males	56	34	28
Total	115	63	48
NO ANEURYSM SERIES			
Females	136	25	4
Males	130	20	4
Total	266	45	8

Case no.	Location and size of aneurysm			Times of recurrence after 1st haemorrhage: weeks 1	2	3	4	5	6	7	8	months 3	4	5	6	7—12	Later recurrences and interval					
1	Int.carotid	2			○	┼																
2	Int.carotid	2						●	+													
3	Carotid bifurc	1					●	┼									4 years	●	1½ years	+		
4	Int carotid	2															1½ years	+				
5	I t carotid	1					○										2½ years	○	2 months	+		
6	Int.carotid	3									●											
7	Ant communic	1		●	┼												4 years	●	1 month	●	3 week	┼
8	Ant.communic	3	F l																			
9	A t.communic	0						○			+											
10	A t communic	1	t			●		┼									6 years	○	10 days	+		
11	A t communic	1	h														6 years	○	1 week	●	5 years	┼
12	A t.communic.	3															4 years	┼				
13	Ant.communic	2	m			●						○										
14	Middle cerebral	1			●	┼																
15	Middle cerebral	2				●	●	┼														
16	Middle cerebral	1	b	●										○								
17	Middle cerebral	0	g			●	┼															
18	Middle cerebral	1		●												+						
19	Post.cerebral	0										○	┼									
20	I t.carotid bilat.	3 1													○		13 years	○	4 years	+		
21	Int.carotid bilat	3 2										○				┼						
22	Middle cer bilat	3 1															4 years	●	6 months	┼		
23	Pericallosal and middle cerebral	2 2						●					+									

○ = non verified haemorrhage ● = verified haemorrhage
+ = non verified fatal haemorrhage ┼ = verified fatal haemorrhage

Size of aneurysm: 0 = not know 1 = small
2 = medium 3 = large

23 had a third haemorrhage (66 per cent), and 16 died 1 died of another disease. Thus the mortality in the third haemorrhage was 70 per cent of the patients at risk (16 out of 23) Of the 6 patients who survived the third haemorrhage from the ruptured aneurysm all died from the fourth haemorrhage (100 per cent) The total mortality from recurrence of haemorrhage was 76 per cent (48 patients out of 63 with recurrent haemorrhage)

The total mortality from recurrent bleeding in the whole aneurysm series was 42 per cent (48 out of 115 survivors after the first haemorrhage)

The time of the first recurrence in the aneurysm series is seen in Table 3 The patients are grouped according to the location of the aneurysm Patients with multiple aneurysms are collected in a separate group because in most instances the offending aneurysm was not known. In 39 cases the first recurrent bleeding occurred within the first 8 weeks after the primary haemorrhage (62 per cent) and in 26 of them within the first 4 weeks (41 per cent of 63 patients who had a second attack) Five patients suffered a second attack within the 3rd to the 12th month but even after 1½—9 years interval a first recurrent bleeding occurred in 19 cases (30 per cent)

The mortality from the first recurrent bleeding in relation to the time interval after the first haemorrhage is also presented in Table 3 Out of the 39 patients who had a recurrent haemorrhage within 8 weeks 13 died but the second haemorrhage proved to be no more benign in cases where the time interval was longer as there were 13 deaths among the 24 patients who had recurrences later than 2 months after the primary haemorrhage. Out of the total of 26 patients who died from their second haemorrhage 11 had lived a normal life for longer than 2 years after the first bleeding Three patients suffered a fatal recurrent bleeding from the rupture of an aneurysm which had remained symptomfree for even as long as 5 7 and 8 years, respectively

More than one recurrent bleeding occurred in 23 patients with aneurysm. The time interval and mortality from recurrent bleeding is presented in Table 4 where also the location and the size of the aneurysms can be seen. In 12 cases the second recurrence occured within 4 weeks after the first one (52 per cent) but even a 15 years interval was recorded A third recurrent bleeding occurred in 3 patients within 8 weeks after the previous haemorrhage; however in the remaining 3 patients the interval was much longer (4 years, 4 years and 5 years)

As stated previously the mortality in multiple attacks is very high and the time interval does not seem to play any part in it, long or short intervals between the attacks have no prognostic significance

Recurrent haemorrhage and mortality from recurrence in the no aneurysm series is presented in Table 2 and Fig 2. Recurrences occurred in 15 cases of 266 surviving patients (17 per cent) 4 of them died from the second bleeding A third bleeding occurred in 8 patients, 3 of them died Three of the surviving 5 patients had a fourth recurrence, and 1 died The total mortality from recurrent haemorrhage in this series was 8 out of 266 (3 per cent) or 18 per cent of 45 patients with a recurrent bleeding

TABLE 6

Interval and mortality of multiple attacks of subarachnoid haemorrhage
9 patients without proven aneurysm

Case no.		Weeks								Months after 1st haemorrhage										Later recurrences and interval			
		1	2	3	4	5	6	7	8	3	4	5	6	7	8	9	10	11	12				
1	1st haemorrhage									○										11 months	○	1 year	+
2		○	○																				
3			○																	2 years	+		
4		○	○	●																			
5																				4½ years	●	1 month	✚
6													○							2½ years	○		
7							●													3 years	○		
8		○	○																				
9				●	✚																		

○ non verified recurrence
● erified recurrence
+ non verified fatal recurrence
✚ erified fatal recurrence

chi square = 56.676 for recurrence and
chi square = 96.061 for mortality

Summary In a series of 115 patients with intracranial aneurysm who had survived their initial attack of subarachnoid haemorrhage 55 per cent had on or more attacks of recurrent bleeding 42 per cent of all the patients, or 76 per cent of the patients who had recurrence of the subarachnoid haemorrhage succumbed in the bleeding. 62 per cent of the recurrences occurred within 8 weeks after the first haemorrhage and 41 per cent within the first 4 weeks. 30 per cent of the recurrences occurred as late as 1½—9 years after the first haemorrhage

The incidence of recurrent bleeding was much lower in the no aneurysm series, the percentage being 17 and 3 per cent died The first recurrent bleeding occurred within 8 weeks in 56 per cent, and in 30 per cent after an interval of 1—14 years.

The time interval between the initial attack and the recurrent haemorrhages followed roughly the same pattern in both series. More than a half of the recurrent haemorrhages occurred within the first 8 weeks, but about a third of them occurred as lat as after an interval of 1—14 years.

The conclusion may be drawn that a recurrent haemorrhage in the aneurysm series is a very ominous sign The first 8 weeks after the first attack of subarachnoid bleeding seems to be the most dangerous period, but this does not mean that thereafter the patients are completely out of danger of dying from subarachnoid haemorrhage as about a third of them have a further subarachnoid bleeding one to several years later

The present series shows that the mortality rate of patients with proven intracranial aneurysms is more than ten times higher than that of patients having subarachnoid haemorrhage without demonstrable intracranial vascular lesions

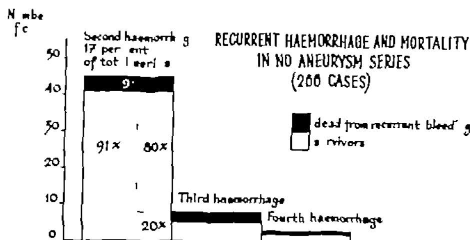


Fig. 2.

TABLE 5

Interval and mortality of first recurrence
45 patients without proven aneurysm

Weeks								Months					Years after 1st haemorrhage							
1	2	3	4	5	6	7	8	3	4	5	6	7—12	1—1½	2	3	5	6	10	14	several
	7	4	1	—	3 (1)	—	3	3 (1)	—	1	1	1	1	5 (2)	3	1	1	1	1	1
25 (1)								6 (1)					14 (2)							

(Number of fatal recurrences in brackets)

The time of the first recurrence in the no aneurysm series is presented in Table 5. 25 patients had their recurrent bleeding within 8 weeks after the primary haemorrhage (56 per cent), 6 (13 per cent) within the 3rd to the 12th month and 14 (31 per cent) had their recurrent bleeding 1—14 years after the initial attack.

The time interval between the initial attack and the fatal cases of first recurrent bleeding is also presented in Table 5. The interval varied between 6 weeks and 2 years.

More than one recurrent bleeding occurred in 9 patients. The time interval between the attacks is presented in Table 6. In 4 patients two or three further bleedings occurred within 8 weeks after the first attack. The longest interval between the second and third bleeding was 5 years.

A comparison between the aneurysm series and the no aneurysm series appears in Table 2, which shows a much higher incidence of recurrences of bleeding and a higher mortality in the former than in the latter.

In order to investigate statistically the general bearing of the results, the figures were subjected to the chi square test (CRAMER 1961). The difference proved to be highly significant in both instances.

subarachnoid bleeding, all of them being alive after a follow-up period which varied between 1 and 12 years. The figures were as follows (see p. 30).

Höök (1958 a) reported 65 survivors in his series of 152 patients. 33 of the patients (52 per cent) reported that they were fully able to work, 7 had mild residual symptoms with only slightly reduced working capacity 14 had more or less severe impairment and 10 were completely disabled.

The morbidity among surviving patients with a ruptured *intracranial aneurysm* not surgically treated has been reported in only few publications.

Logue (1956) followed up patients with aneurysm of the anterior cerebral or anterior communicating arteries. 63 patients were treated conservatively 20 of them survived. Four had serious neurological defects (1 was demented and hemiplegic; 1 had a permanent memory defect and was unable to work, 2 had hemiparesis and dysphasia but were able to work to some extent) 16 had returned to work but some of them complained of giddiness and headache.

af Björkesten & Troupp (1957) reported that in their series of 40 patients, 5 out of the 18 survivors were completely disabled; 3 had impaired working capac ity 3 were incapacitated for other reasons, and 7 had complete working capac ity Thus 8 out of 18 survivors were more or less disabled due t the bleeding from the ruptured aneurysm.

McKissock *et al.* (1960 b) found that out of 48 patients in their conservatively treated aneurysm series 28 made various degrees f recovery 19 of these were able to return to f ll work, 6 were partially disabled and fit for light work; and 2 were totally disabled. One more patient was alive but his condition was unknown. All of them were followed up for at least six months, most of them for a year or more.

The following morbidity figures for subarachnoid haemorrhage patients *without proven aneurysm* ha e been taken from previous writers.

Dinsmore & Polcyn (1956) reported that 52 out of 71 survivors returned to normal life without showing any residual symptoms at all. Four were under medical care for hypertension but were active within the limits of their hypertension. Two had sufficient deficit to prevent work, and one had psychotic episodes which antedated the bleeding and reappeared 2 years after it.

In the no aneurysm series of af Björkesten & Troupp (1957) 33 patients out of the total number of 61 were work ing normally 13 had an impaired work ing capacity and 3 were fully incapaci tated because of sequelae f the bleeding; 9 patients were disabled due to another unrelated disease.

In Höök s (1958 b) series 80 out of 122 surviving patients (67 per cent) — 2 could not be traced — were entirely symptom free and able to work. 27 (22 per cent) had slight residual symptoms, reducing their working capacity slightly or not at all; and 13 (11 per cent) considered themselves completely incapacitated. In the latter group 3 or possibly 4 patients were disabled due to an unrelated disease

The division of the surviving patients of the *present series* according to symptoms into the groups shown in Tables 7 and 8 is more or less arbitrary and, of

3. MORBIDITY

In discussing the prognosis of subarachnoid haemorrhage it is important to consider in addition to the mortality the condition of the patients who survive one or more attacks of subarachnoid bleeding how many of them regain full working capacity and how many are partially or completely crippled and unable to earn their living

MAGEE (1943) reported that among the 66 survivors in his series of 150 patients with subarachnoid bleeding, only 45 had normal working capacity 21 (32 per cent) being partially disabled He examined 22 patients 6 months to 4 years after discharge from the hospital and only three had nothing to complain of

WOLF *et al* (1945) had 30 survivors out of 46 patients with subarachnoid bleeding 3 out of these 30 patients had severe neurological sequelae.

HAMBY (1948 1952) reported that 48 survivors were known to be alive at the time of follow up 21 were well, 13 were working with handicaps, 11 were neurological cripples; thus only 16 9 per cent of the total of 130 patients with subarachnoid haemorrhage were well and had full working capacity

ASK UPMARK & INGVAR (1950) stated that out of 64 survivors approximately 50 per cent considered themselves able to carry on their occupation as usual, the rest were more or less crippled

HYLAND (1950) reported that 46 survivors could be traced at the time of follow up 43 were able to work, although 14 of these had mild or moderate disability 3 of the patients remained completely crippled

WOLFE (1953) was able to trace only 29 of his 41 survivors, 23 were alive at the time of follow up and 11 of these had severe sequelae of the original illness (hemiplegia in 4 cases, dementia in 3 headaches in 3, visual field defect in one).

JACOBSON (1954) reported that in his series collected from several publications in the literature there were 990 patients with spontaneous subarachnoid haemorrhage whose condition at follow up was mentioned. A total of 93 patients were moderately to severely damaged by significant residual disorders such as hemiplegia, monoplegia dementia personality changes and neurotic manifestation to the point of disability etc. this gives a percentage of 9 4 of all the patients with subarachnoid haemorrhage

WALTON (1956) reported the condition and working capacity of 120 patients with

	Percentage of survivors		Percentage of total series	
Full employment	79/120	65.8	79/312	25.3
Lighter occupation	24/120	20 0%	24/312	7 8
Retired, but active	12/120	10 0%	12/312	3.8
Unable to work	5/120	4.2 %	5/312	1 6 %
Completely well	36/120	30.0%	36/312	11.5
Slight sequelae	40/120	33.3%	40/312	12.8
Moderate or severe sequelae	39/120	32.5%	39/312	12.6
Completely disabled	5/120	4.2 %	5/312	1 6

in the aneurysm series is presented in Table 7. There were 60 survivors at the time of follow up. 21 of them (40 per cent) reported that they had full working capacity and only very minor symptoms persisting after the subarachnoid haemorrhage: these symptoms did not disturb their normal life. 28 patients were partially disabled, 21 of them due to the haemorrhage. 5 had neurological sequelae such as hemiplegia, monoplegia or epilepsy and 12 were partially incapacitated due to diffuse cerebral symptoms such as headache, dizziness, unusual tiredness or mental disturbances. In the remaining patients combinations of the above mentioned symptoms were reported to be the cause of partial disability. 8 patients were totally disabled: 4 had severe neurological residua and 2 diffuse cerebral symptoms, whereas 2 patients were disabled because of an unrelated disease. Thus altogether 27 patients out of 60 survivors (45 per cent) were partially or totally incapacitated due to the aneurysmal subarachnoid bleeding.

The condition of the 250 surviving *patients without proven aneurysm* is presented in Table 8. 145 patients were able to return to their usual work without any handicaps, the percentage being 58. 71 patients were partially disabled due to neurological residua (9) or diffuse cerebral symptoms (49) or combinations (13). 12 patients were totally disabled due to sequelae of the subarachnoid haemorrhage. In 22 patients the cause of disability was some unrelated disease. Thus altogether 33 per cent (83 out of 250 survivors) were partially or totally disabled due to the subarachnoid haemorrhage.

A comparison between the aneurysm and the no aneurysm series showed a higher incidence of disability in patients of the aneurysm series than in those of the no aneurysm series. Statistically the difference proved to be almost significant, chi square = 4.772.

Because the degree of the patients' disability was mostly based on information which they themselves had provided, a more objective method of assessing their working capacity was sought. This was provided by enquiring which patients were receiving disability pensions from the National Pensions Institute as a result of their subarachnoid haemorrhage.

TABLE 8

Condition of 250 surviving patients without proven aneurysm

	Total number of cases	Patients' condition at follow up													
		Normal working capacity	Partial disability because of						Total disability because of						
			Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total	Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total
Males	123	70	2	2	22	4	12	43	3	—	2	1	4	10
Females	127	75	7	3	26	4	5	45	2	1	—	3	1	7
Total	250	145	9	5	49	8	17	88	5	1	2	4	5	17

3 — Tappura

course affected by the author's personal impression of the patients' condition at the time of follow up.

Also the fact that only a minor section of the patients were seen in the hospital at the time of the follow up makes the information less descriptive and the judgement of the patients' symptoms more or less uncertain.

The patients were classified as partially disabled if they reported having symptoms or signs attributable to the previous subarachnoid haemorrhage but were able to do their usual work or lighter occupation. Patients who were not able to do any work were classified as totally disabled.

The »neurological signs» group consisted of patients who had neurological deficits in the form of hemiplegia or hemiparesis at some stage of their illness and still had clear-cut residua at the time of follow up. In addition, patients who had epilepsy evidently initiated by the subarachnoid haemorrhage, were grouped under this heading. Cranial nerve palsies were not included; patients with ophthalmoplegia will be dealt with separately and other cranial nerves were extremely seldom involved.

»Diffuse cerebral symptoms» which formed the main group of symptoms causing disability of the patients, were symptoms which were more or less vague, mostly subjective, and of either cerebral or psychic origin. The majority of patients with these symptoms complained of headaches, intermittent or constant, often accompanied by severe dizziness; these symptoms prevented patients from more strenuous work.

Some of these patients could not be placed under one heading only; thus, in Tables 7 and 8 mixed groups are presented, consisting of patients with disabling symptoms or signs originating from different sources. These difficulties in grouping the patients reduced the numbers in every group and it was difficult to draw any clear conclusions. Thus it seemed justifiable for statistical purposes to collect all the patients into two groups, patients with normal working capacity and patients with disability. Patients who had symptoms caused by other unrelated diseases were excluded, unless they also had symptoms caused by subarachnoid bleeding.

The condition of the surviving patients

TABLE 7

Condition of 60 surviving patients with aneurysm

	Total number of cases	Patients' condition at follow up													
		Normal working capacity	Partial disability because of						Total disability because of						
			Neurological sign		Diffuse cerebral symptom		Unrelated disease	Total	Neurological signs		Diffuse cerebral symptom		Unrelated disease	Total
Males	24	11	1	1	5	1	2	10	1	—	1	—	1	3
Females	38	13	4	—	7	2	5	18	3	—	—	1	1	5
Total	60	24	5	1	12	3	7	28	4	—	1	1	2	8

in the aneurysm series is presented in Table 7 There were 60 survivors at the time of follow up 21 of them (40 per cent) reported that they had full working capacity and only very minor symptoms persisting after the subarachnoid haemorrhage these symptoms did not disturb their normal life 28 patients were partially disabled 21 of them due to the haemorrhage. 5 had neurological sequelae such as hemiplegia, monoplegia or epilepsy and 12 were partially incapacitated due to diffuse cerebral symptoms such as headache, dizziness, unusual tiredness or mental disturbances. In the remaining patients combinations of the above mentioned symptoms were reported to be the cause of partial disability 8 patients were totally disabled; 4 had severe neurological residua and 2 diffuse cerebral symptoms, whereas 2 patients were disabled because of an unrelated disease. Thus altogether 27 patients out of 60 survivors (45 per cent) were partially or totally incapacitated due to the aneurysmal subarachnoid bleeding.

The condition of the 250 surviving *patients without proven aneurysm* is presented in Table 8. 145 patients were able to return to their usual work without any handicaps, the percentage being 58. 71 patients were partially disabled due to neurological residua (9) or diffuse cerebral symptoms (49) or combinations (13). 12 patients were totally disabled due to sequelae of the subarachnoid haemorrhage. In 22 patients the cause of disability was some unrelated disease. Thus altogether 33 per cent (83 out of 250 survivors) were partially or totally disabled due to the subarachnoid haemorrhage.

A comparison between the aneurysm and the no aneurysm series showed a higher incidence of disability in patients of the aneurysm series than in those of the no aneurysm series Statistically the difference proved to be almost significant chi square = 4.772.

Because the degree of the patients disability was mostly based on information which they themselves had provided, a more objective method of assessing their working capacity was sought. This was provided by enquiring which patients were receiving disability pensions from the National Pensions Institute as a result of their subarachnoid haemorrhage.

TABLE 8

Condition of 250 surviving patients without proven aneurysm

	Total number of cases	Patients' condition at follow up												
		Normal working capacity	Partial disability because of						Total disability because of					
			Neurological signs		Diffuse cerebral symptoms		Unrelated disease	Total	Neurological signs		Diffuse cerebral symptoms		Unrelated disease	Total
Males	123	70	2	2	23	4	12	43	3	—	2	1	4	10
Females	127	75	7	3	26	4	5	45	2	1	—	3	1	7
Total	250	145	9	5	49	8	17	88	5	1	2	4	5	17

1 — Tappara

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Also the fact that only a minor section of the patients were seen in the hospital at the time of the follow-up makes the information less descriptive and the judgement of the patients' symptoms more or less uncertain.

The patients were classified as partially disabled if they reported having symptoms or signs attributable to the previous subarachnoid haemorrhage but were able to do their usual work or lighter occupation. Patients who were not able to do any work were classified as totally disabled.

The »neurological signs» group consisted of patients who had neurological deficits in the form of hemiplegia or hemiparesis at some stage of their illness and still had clear-cut residua at the time of follow-up. In addition, patients who had epilepsy evidently initiated by the subarachnoid haemorrhage, were grouped under this heading. Cranial nerve palsies were not included; patients with ophthalmoplegia will be dealt with separately and other cranial nerves were extremely seldom involved.

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The condition of the surviving patients

TABLE 7

Condition of 60 surviving patients with aneurysm

	Total number of cases	Patients' condition at follow-up												
		Normal working capacity	Partial disability because of						Total disability because of					
			Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total	Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total
Males	24	11	1	1	6	1	2	10	1	—	1	—	1	3
Females	36	13	4	—	7	2	5	18	3	—	—	1	1	5
Total	60	24	5	1	12	3	7	28	4	—	1	1	2	8

In the literature there are a number of reports concerning the influence of age on the prognosis for *patients with intracranial ruptured aneurysms*. McKissock & Walsh (1956) found that the mortality was 44 per cent for patients under 50 years of age and 67.5 per cent for patients over 50 years; their series consisted of 108 conservatively treated patients with aneurysms, af Bjorkesten & Troupp (1957) reported that in their aneurysm series of 40 patients 6 patients out of 7 with normal working capacity were under 40 years of age at the time of bleeding; whereas 4 patients out of 5 that were completely incapacitated were past 40 years at the time of bleeding. They did not comment on the correlation between age and mortality McKissock *et al* (1960 b), in their report on patients with posterior communicating aneurysms treated conservatively considered that age had a doubtful significance for the prognosis. They had 19 patients under 50 years of age 10 of whom died and 29 patients over 50 with 10 deaths.

In their *no aneurysm series* of patients, Dunsmore & Polcyn (1956) did not find any influence of age on the prognosis. On the other hand Höök (1958 b) reported that 9 patients with severe neurological symptoms were all more than 40 years of age. Levy (1960) also stated that increased age generally meant a worse prognosis.

The age and sex distribution *in the present series* is shown in Fig. 3. In the aneurysm series there were 62 females and 58 males. The average age of these patients at the time of the first attack of subarachnoid haemorrhage or ophthalmoplegia was 42.1 years (females 43.3 years, males 40.8 years). The youngest patient was 17 and the oldest 70 years of age.

In the no aneurysm series there were 136 females and 131 males. The average age at the time of the first attack of sub-

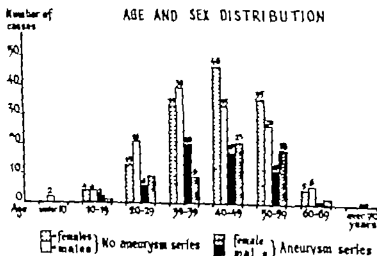


Fig. 3.

The information thus obtained showed that a small proportion of patients regarding themselves as disabled in fact received pensions. Of the 6 patients of the aneurysm series who considered themselves to be totally disabled by their haemorrhage 5 were receiving pensions. Of the 12 corresponding patients in the no aneurysm series 5 also were receiving pensions. Of the 21 patients in the aneurysm series who considered themselves to be partially disabled only 8 were receiving pensions, whilst the corresponding figures in the no aneurysm series showed that of the 71 patients only 17 received pensions.

Nevertheless these figures do not conclusively establish whether the low incidence of patients receiving pensions was because they had exaggerated their incapacity, or whether they simply had never applied for a pension as for example those who were unemployed such as housewives.

Summary. Analysis of the cases of the surviving patients in these series suggests the conclusion that a subarachnoid haemorrhage originating from a demonstrable intracranial aneurysm affects the condition of the surviving patients more than does a bleeding coming from an unknown source. The degree of the disability does not vary notably in these two series, which however are too limited to allow of any definite conclusions. It is logical to assume that if the subarachnoid haemorrhage even in the »no aneurysm» series originates from a small aneurysm or minute arteriovenous malformation which is not demonstrable, the bleeding will be on the whole less profuse; thus, the lesions caused by the haemorrhage directly or by the vasospasm will be minor and in many cases transitory. On the other hand bleeding originating from a large aneurysm will be more profuse and will last longer causing larger cerebral lesions, with subsequent graver effect on the condition of the surviving patients.

B. FACTORS INFLUENCING PROGNOSIS

I. AGE AND SEX

a. AGE

The influence of age on the prognosis for patients with subarachnoid bleeding has been reported variably in the literature. Many authors, for example STRAUSS & TARACHOW (1937), SAHS & KEIL (1943), HYLAND (1950), WOLFE (1953) and MAGLADERY (1955), have reported a higher mortality rate in older persons. In MAGLADERY's series the mortality was 58 per cent for patients over 50 years of age and 41 per cent for patients under 50 years. WALTON (1956) and HOOK (1958 a) also reported that there was an increase in the death rate with increasing age in both sexes. On the other hand, ROWLEY *et al.* (1958) gave the opinion that the mortality rate was slightly higher in patients of 30—60 years (52.8 per cent) than in the older age group (over 60 years), the percentage in the latter being 47.2. HAMBY (1948, 1952) reported that, as regards prognosis, age was not a determining factor. In his series, the average age of the patients who recovered was 45 years, and of those who died 48.4 years. In JACOBSON's (1951) series too, collected from the literature, age had no prognostic significance.

arachnoid haemorrhage was 41.2 years (females 42.3 males 40.2 years). The youngest patient was 3 and the oldest 67 years of age. Consequently the series were *quite* similar with regard to age.

The number of recurrent haemorrhages and mortality in recurrence in different age groups is shown in Fig. 4 for the aneurysm series and in Fig. 5 for the no aneurysm series.

In order to investigate the frequency of recurrent haemorrhages and mortality in recurrence in relation to age the patients were divided into two groups: patients under 40 years of age and patients over 40 years of age. In the literature the borderline varies between 50 years of age (MAGLADERY, MCKISSOCK & WALSH, MCKISSOCK *et al.*) and 40 years of age (AF BJORKESTEN & TROUPP, HÖÖK). The age of 40 was preferred in the present series because it seemed to divide the groups more evenly than did the age of 50.

The results are shown in Table 9. *In the aneurysm series* there were 44 patients under 40 years of age. 29 of these had recurrent haemorrhages, that is 66 per cent of all the patients under 40 years of age. In the older group the number of patients with recurrent haemorrhage was 34 out of 71 patients over 40 years of age, which is 48 per cent of all the patients over 40 years of age.

The mortality in recurrent haemorrhage in the two age groups of the aneurysm series was as follows. 23 out of 44 patients under 40 years of age and 25 patients out of 71 patients over 40 years of age died from recurrent haemorrhage. Thus the mortality in the younger group was 52 per cent of the total number of patients under 40 years and 79 per cent of all the patients who had had recurrent haemorrhages. In the older age group the corresponding percentages were 35 and 74.

Compared, the percentages seem to show that patients under 40 years of age had a slightly poorer prognosis than those in the older age group. However statistical analysis with the chi square test showed that the influence of age on the incidence of recurrent haemorrhage and

TABLE 9

Number of patients with recurrence of haemorrhage, and mortality in recurrence correlated to age at first attack

	Age at first attack	Total number of cases	Patients with recurrent haemorrhage		Deaths from recurrence		
			Number	Per cent	Number	Per cent of total number	Per cent of recurrences
ANEURYSM SERIES	Under 40	44	29	66	23	52	79
	Over 40	71	34	48	25	35	74
	Total	115	63	55	48	42	76
NO ANEURYSM SERIES	Under 40	115	19	16	3	3	20
	Over 40	151	24	17	5	3	30
	Total	266	43	17	8	3	20

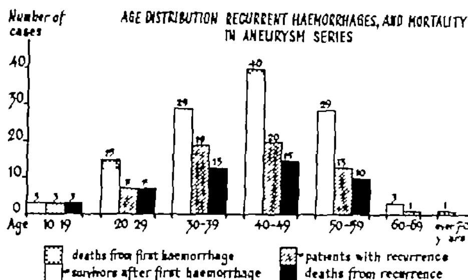


Fig. 4

Number of cases
AGE DISTRIBUTION, RECURRENT HAEMORRHAGES, AND MORTALITY IN NO ANEURYSM SERIES
80
70
60
50
40
30
20
10
0
Age 10 under
10-19
20 29
30 39
40-49
50-59
60-69 years
2
8 1
34 4
72 14 3
79 16 1
61 10 4
11
deaths from first haemorrhage
survivors after first haemorrhage
patients with recurrence
deaths from recurrence

Fig 5.

TABLE 11

Condition of patients at follow up correlated to age at first attack of bleeding

	Age at first attack	Total number of cases	Number of cases evaluated	Normal working capacity	Partial disability	Total disability
ANEURYSM	Under 40	47	20	11	8	1
	Over 40	73	31	13	13	5
	Total	120	51	24	21	6
NO ANEURYSM SERIES	Under 40	116	106	77	23	5
	Over 40	161	122	67	48	7
	Total	267	227	144	71	12

series divided into age groups and the condition of the survivors at the time of follow up As regards the patients who died from unrelated diseases, there was not information enough about their condition during the follow-up period, and so they had to be excluded.

As there was a considerable amount of scatter in the different age groups it was difficult to assess the infl ence of age. The most that could be expected was approximate results from larger groups. Consequently the series were again split int two groups with a dividing line of 10 years of age The results are shown in Table 11 *In the aneurysm series* th younger age group contained 47 patients, 11 working normally 8 partially disabled du to neurological handicaps or diffuse cerebral symptoms, and 1 totally disabled *because of diffuse* cerebral ymptoms. In the older group of 73 patients 13 had normal working capacity 13 had *partial disability* due to the illness and 5 were totally disabled. As these *figures* are ery small the percentages were not calculated but the results were subjected to the hi square test. In order to btain larger groups the comparison in both age groups was made between patients with normal working capacity and patients with disability partial or total. The results showed that the influence of age on the condition of the surviving patients was not significant.

In the no aneurysm series the younger age group contained 77 patients who were working normally· 23 were partially disabled and 5 totally disabled because of neurological handicaps or diffuse cerebral *symptoms. In the* older age group there were 67 patients working normally· 48 were partially disabled and 7 totally disabled.

The chi square test showed that in this group of patients older *people* were more handicapped than the younger ones by the sequelae of subarachnoid haemorrhage. Statistically the difference was significant. chi square = 8.536.

Summary The highest incidence of subarachnoid *haemorrhage in both the* aneurysm and the no aneurysm series occurred in the third and fourth decade *of life the* mean being just over 40 years.

Age did not influence the number of recurrent haemorrhages, or mortality In the *no aneurysm series the* condition of people in the older group was affected more than *that of* people in the younger group

on the mortality in recurrence was not significant.

The patients *in the no aneurysm series were treated similarly* The results are also shown in Table 9 There were 115 patients under 40 years of age, 19 of these (16 per cent) had recurrent haemorrhage. In the older group there were 151 patients, 26 had recurrences, forming 17 per cent of all the patients over 40 years of age. *The difference was statistically not significant.*

The mortality figures were 3 in the younger age group and 5 in the older As these figures are so small the percentages, 20 per cent and 30 per cent, do not give evidence enough for comparison

The influence of age on the condition of the surviving patients has been analyzed very little in the previous literature, apart from the previously mentioned *investigations of* AF BJÖRKESTEN & TROUPP and HÖÖK Even in these reports the figures are exceedingly small. One would naturally expect older people to be more affected than younger ones by the lesions caused by subarachnoid haemorrhage

Table 10 shows the patients in both

TABLE 10

Influence of age on prognosis

Patient condition at follow up

	Age groups	Number of cases	Normal working capacity	Partial disability because of: Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total	Total disability because of: Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total	Deaths and cause of death
ANEURYSM SEREIS	10—19	3														3 RH
	20—29	15	5													3 FH 7 RH
	30—39	29	6	3	1	2	2		8			1			1	13 RH 1 UD
	40—49	10	0	1		5	1	3	10	3			1	2	6	1 FH 13 RH 1 UD
	50—59	29	1	1		5		2	8							12 RH 5 UD
	60—69	3						2	2	1					1	
	70—	1														1 FH
		120	21	5	1	12	3	7	28	4		1	1	2	8	5 FH 48 RH, 7 UD
NO ANEURYSM SERIES	0—9	2	2													
	10—19	8	6					1	1					1	1	
	20—29	34	30	1		2		1	4							
	30—39	72	30	3	3	13	1	1	21	2	1	1	1	1	6	1 FH 3 RH 2 UD
	40—49	79	41	3	1	14	5	6	20	1		1	2	2	6	2 RH 1 UD
	50—59	61	23	2	1	16	2	4	27	2			1		3	3 RH 4 UD
	60—69	11	3			2		4	6					1	1	1 UD
		267	145	9	5	49	8	17	88	5	1	2	4	5	17	1 FH 8 RH 8 UD

FH = 1st haemorrhage
RH = Recurrent haemorrhage
UD = Unrelated disease

where the haemorrhage is an extension of an originally intracerebral haematoma.

Odom *et al.* (1952 b) reported that only about 25 per cent of spontaneous intracranial haematomas failed to contaminate the subarachnoid space. In their series of 55 cases of hypertensive and arteriosclerotic patients with intracerebral haematoma 41 also had blood in the spinal fluid, most of these patients, however were autopsy cases.

Before a diagnosis of arterial hypertension can be made certain criteria have to be fulfilled. In many cases the history of a pre-existing hypertension is difficult to obtain, because the patients very often come to the hospital *in extremis* and accurate information is not available. A measurement of high blood pressure taken during the bleeding is of no significance, because increased intracranial pressure is mostly accompanied by high arterial blood pressure. Clinically the diagnosis of hypertension is often very difficult without meticulous and repeated measurements of the systolic and diastolic blood pressure, which in most cases have not been performed. The most reliable evidence of existing hypertension can only be obtained at the autopsy.

The borderline above which the blood pressure is considered pathological varies in different publications. Cecil & Loeb (1959) stated that in the adult an elevation of systolic pressure above 140 mm.Hg may be termed systolic hypertension and elevation of the diastolic to 90 mm.Hg or above may be regarded as diastolic hypertension. Clinically the latter is more important. Johansson (1961) gave the following border zones for patients under 40 years of age 150—160/90—95; for patients of 40 to 60 years of age 165—180/95—100 and for patients of more than 60 years of age 180—190/100—105. According to him only patients whose blood pressure is over these border zones are to be considered hypertensive.

Sands & Keil (1943), Hamby (1948, 1952) Hyland (1950) Wolfe (1953) and Magladery (1955) stated that the hypertensive patient with subarachnoid haemorrhage had a poorer prognosis than the normotensive one. Hamby did not, however consider hypertension a very important factor: in his non-differentiated series hypertension was present in 21 per cent of the survivors and in 21 per cent of the patients who died. Walton (1956) also considered the significance of hypertension to be probable in relation to mortality. In his series hypertension was present in 101 cases out of 312; 68 of these 101 patients died. Rowley *et al.* (1957) had 52 hypertensive patients out of 157 patients with subarachnoid haemorrhage, and 30 of them died. 41 of the remaining 105 patients died, thus the mortality in the hypertensive group was higher. Among the 152 patients in Höök's (1958 a) non-differentiated series 70 per cent had reasonably dependable data on blood pressure. Hypertension — a systolic pressure equal to or in excess of 175 mm.Hg and/or diastolic pressure of 100 mm.Hg or higher — was diagnosed in 36 cases and suspected in an additional 10. Höök stated that it might be difficult to obtain reliable information about hypertension in patients with subarachnoid haemorrhage. Some patients die before any history can be obtained, and as hypertensive patients often belong

b. SEX

The influence of sex has been reported by ASK UPMARK & INGVAR (1950) among others. According to these investigators, the female sex is more apt to get subarachnoid haemorrhage, and the illness is more fatal in women WALTON (1956) also stated that there was a suggestion of the female death rate being higher but the difference was not significant. On the other hand ROWLEY *et al* (19o7) reported that men were more often affected than women the mortality of men in their series was 52.2 per cent and that of women 10 per cent.

The mortality in recurrent haemorrhage for both sex groups can be seen from Table 2 (p 24) 29 females in the aneurysm series had a recurrence of subarachnoid bleeding 20 of them died 31 males had a recurrence, and 28 died The corresponding numbers in the no aneurysm series were as follows 25 females and 20 males had a recurrence 8 of them died 4 in each group.

The chi square test showed that there was no significant difference between females and males.

The correlation between sex and morbidity is presented in Table 12. The series were divided into normally working patients and patients with partial or total disability The chi square test showed that there was no significant difference between females and males. This is a noteworthy result in consideration of disability One would expect the more demanding work of men, mostly taking place outside their homes and demanding skill and ability for good results, to warrant a comparatively larger disability in men.

Summary In the aneurysm and no aneurysm series females and males were represented in about the same proportion, and sex did not influence the number of recurrent haemorrhages, mortality in recurrence, or morbidity

2. CONCOMITANT DISEASES

The influence of *hypertension* on the prognosis of subarachnoid haemorrhage has been commented on in several investigations. The high pressure against the arterial wall and the pathological changes thus caused in the different layers of the vessels have been considered in discussing the development and subsequent rupture of aneurysms. On the other hand the part played by hypertension also has to be taken into consideration as an etiological factor in cases of subarachnoid haemorrhage where no vascular abnormalities are to be found in the angiograms, or

TABLE 12

Condition of patients at follow up correlated to sex

	Sex	Total number of cases	Number of cases evaluated	Normal working capacity	Partial disability	Total disability
ANEURYSM SERIES	Females	62	38	13	18	
	Males	58	24	11	10	3
NO ANEURYSM SERIES	Females	138	127	75	45	7
	Males	131	123	70	43	10

TABLE 13

Number of patients with recurrence of haemorrhage and mortality in recurrence correlated to blood pressure

	Blood pressure	Total number of cases	Patients with recurrent haemorrhage		Deaths from recurrence		
			Number	Per cent	Number	Per cent of total number	Per cent of recurrences
ANEURYSM SERIES	Over 150 mm Hg	48	15	31	13	27	87
	Under 150 mm.Hg	64	46	72	33	52	72
	Not known	3	2		2		
	Total	115	63		48		
NO ANEURYSM SERIES	Over 150 mm.Hg	108	18	16	3	3	16
	Under 150 mm.Hg	157	27	17	5	3	19
	Not known	1					
	Total	266	43		8		

mm.Hg. 15 of them had a recurrent haemorrhage: that is, 31 per cent of all the hypertensive patients in this group 13 of the 15 patients with a recurrence of haemorrhage died (87 per cent) In the normotensive group of 64 patients — those with a blood pressure of under 150 mm.Hg — 46 patients had a recurrence that is, 72 per cent of all the normotensive patients; 33 (72 per cent) of the patients with recurrence died. The blood pressure of 3 patients was not recorded.

The above percentages seem to suggest that a normotensive patient is more liable to have another haemorrhage and the hypertensive patient runs a greater risk of dying from his recurrence of bleeding.

In the no aneurysm series the relation between hypertension and the patients chance of survival was analyzed similarly (Table 13). There were 108 patients who were classified as hypertensive according to the grouping used above, thus 41 per cent of all the patients in this group had a blood pressure of over 150 mm.Hg 18 of them, or 16 per cent, had recurrences of haemorrhage; 3 of these patients died from their recurrence (16 per cent). In the normotensive group of 157 patients the corresponding figures were 27 patients with recurrences of bleeding (17 per cent) and 5 deaths (18 per cent). The blood pressure of one patient was not mentioned.

The percentages here do not reveal much difference in any *direction. The* statistical analysis also showed that the difference between the hypertensive and normotensive group in regard to *recurrence of haemorrhage* and mortality was not significant.

The condition of the hypertensive pa

to the older age group other factors often play a part in the prognosis. He gave no prognostic data in respect of hypertension.

The only author to deny an influence of hypertension on the prognosis of subarachnoid bleeding in a non-differentiated *series* was MAGEE (1943)

MCKISSOCK & WALSH (1956) in their *aneurysm series* of 108 patients had a mortality of 45 per cent in 65 normotensive patients and 67.5 per cent in 43 hypertensive patients. They classified patients with a systolic pressure of 160 mm Hg and over and/or a diastolic pressure of 90 mm.Hg or over as hypertensive. In a later report on »posterior communicating« aneurysms MCKISSOCK *et al* (1960 b) concluded that hypertension had a doubtful significance for the prognosis of aneurysm patients.

Evaluation has also been made of the rôle of hypertension in the prognosis of the few series of *patients with no aneurysm* whose data has been published up to now ODOM *et al* (1952 a) had 43 cases in the group of patients with hypertensive cardiovascular disease and arteriosclerosis, and all of them died They stated that in *these cases subarachnoid haemorrhage* was often an extension of an intracerebral haemorrhage, the prognosis of which was mostly grave DUNSMORE & POLCYN (1956) admitted that the rôle of hypertension was difficult to evaluate Using a rigid criterion they classified only 7 patients out of 81 as hypertensive 3 of them were well at the time of follow up and 4 died from recurrence. In neither the aneurysm nor the no aneurysm series of AF BJÖRKESTEN & TROUPP (1957) was any difference found in relation to chance of survival between patients with hypertension — those with a blood pressure of over 150/100 — and patients with normotension. LEVY (1960) divided his 76 patients *with subarachnoid haemorrhage* but without demonstrable vascular lesions into three groups as regards hypertension He had 9 cases which were known to be hypertensive before the attack of subarachnoid bleeding; 19 cases were hypertensive during the attack, and 48 patients were normotensive throughout. Any blood pressure reading over 150/90 or 140/100 was considered elevated He concluded that a preexisting *hypertension was directly related* to the possibility of a fatal outcome also the survival time was shortened in patients with high blood pressure.

In all cases but 9 of *the present series* the blood pressure was measured a week or more after the attack of subarachnoid bleeding thus the influence of high intracranial pressure was considered to be mostly excluded. The 9 patients who were admitted immediately after their episode of bleeding were not hypertensive In most cases the blood pressure was measured only once.

The patients were divided into two groups, patients with a systolic blood pressure of over 150 mm.Hg and patients with a systolic *blood pressure* of under 150 mm.Hg The diastolic blood pressure was not taken into consideration, because unfortunately the measurements were very variable and apparently not always reliable.

The results of the analysis are shown in Table 13. *In the aneurysm series* there were 48 patients (42 per cent) whose systolic blood pressure was over 150

be made due to the small number of patients in the former category

Since hypertension is in general a disease of the older age groups, age might have affected the above conclusion. The hypertensive patients were consequently divided into two age groups, the border line being 40 years of age, as in the previous analysis. The results are shown in Table 15. The statistical analysis did not reveal any significant difference between the two age-groups as regards mortality or disability. Only in the no aneurysm group was there slight evidence that hypertensive patients over 40 years of age were more incapacitated by their illness than were those in the younger age group.

Summary. Hypertension appears to have no significant influence on the prognosis of patients with subarachnoid haemorrhage. The only statistically significant difference between normotensives and hypertensives is to be seen in the no aneurysm series; at the time of follow up the hypertensive patients were more incapacitated by sequelae persisting after their haemorrhage.

Congenital abnormalities. Coarctation of the aorta and polycystic kidney appear to have greater incidence among patients with aneurysm than would be expected in an unselected cross-section of the population (WALTON 1956).

On the other hand it seems possible that hypertension, which nearly always accompanies coarctation of the aorta and polycystic kidney causes the rupture of the aneurysm or possibly even its formation. This probability was discussed by WALTON (1956) and LINDBERG DITLEFSEN & TONJUM (1960) among others.

There were 3 patients in the present aneurysm series with coarctation of the aorta. One of the patients was a 26 year old man with a blood pressure of 185/85; he had had one verified subarachnoid bleeding from one of his two aneurysms, which were on the left pericallosal and right callosomarginal arteries; but he had recovered and was in good condition at the follow up. The second patient, 54 years old was admitted immediately after her haemorrhage; she was in poor condition and died within two days. During her stay in the hospital the blood pressure was 118/70 probably due to shock. A coarctation with a diameter of 2—3 mm. was revealed at the autopsy. The third patient died on the third day from a haemorrhage due to the rupture of an aneurysm on the middle cerebral artery; coarctation of the aorta was found at the autopsy. The blood pressure of this patient was not measured

TABLE 15

Influence of age on prognosis for hypertensive patients

	Age groups	Number of patients with blood pressure over 160 mm Hg	Number of patients evaluated	Condition at follow up			Deaths from haemorrhage
				Normal working capacity	Partial disability	Total disability	
ANEURYSM SERIES	Under 40	9	8	4	2		2
	Over 40	41	30	8	8	3	11
NO ANEURYSM SERIES	Under 40	28	23	16	3	2	2
	Over 40	72	58	20	30	6	2

TABLE 14

Condition of patients at follow up correlated to blood pressure

	Blood pressure	Total number of cases	Number of cases evaluated	Normal working capacity	Disability	
					Partial	Total
ANEURYSM SERIES	Over 150 mm Hg	49	25	12	9	4
	Under 150 mm Hg	68	25	11	12	2
	Not known	*3*	*1*	*1*		
	Total	120	51	24	21	6
NO ANEURYSM SERIES	Over 150 mm.Hg	99	79	33	38	8
	Under 150 mm Hg	167	146	109	33	4
	Not known	1	1	1		
	Total	267	225	143	71	12

tients at follow up compared with the normotensive ones appear from Table 14. There were 25 hypertensive survivors in the aneurysm series, 12 of them were working normally 13 were more of less disabled Out of 25 normotensive surviving patients 11 had normal working capacity 14 were disabled

In the no aneurysm series 33 patients out of 79 hypertensive survivors were working normally 46 had disabling symptoms after their subarachnoid haemorrhage. In the normotensive group of 146 survivors 109 had normal working capacity 37 were more or less disabled.

The chi square test showed that in the *aneurysm series* the difference between the hypertensives and normotensives was not significant, but in the no aneurysm series hypertensive patients were found to be more affected by symptoms and signs originating mainly from the subarachnoid haemorrhage. The difference was highly significant chi square = 22.212.

As the border line at 150 mm Hg was comparatively low the patients with a blood pressure exceeding 200 mm Hg were specially studied

In the aneurysm series there were 9 patients whose systolic blood pressure was over 200 mm Hg Three of these patients died, one from the first haemorrhage and 2 from recurrent *bleeding* Of the 6 survivors, 5 were totally or partially incapacitated whilst 3 of them suffered from symptoms apparently due to *the hypertension.*

In the no aneurysm series there were 14 patients whose systolic blood pressure was over 200 mm Hg Three of these patients died 2 from recurrence and the third from an unrelated disease Eight patients were partially or totally incapacitated 2 of them due to their hypertensive symptoms.

A comparison between *patients whose* blood pressure was over 200 mm Hg with those patients whose blood pressure was under 200 mm Hg could not

(1948, 1952) on the other hand reported that physical signs gave evidence of brain damage but were of no value in estimating the prognosis. In his series of 130 patients with subarachnoid haemorrhage there was hemiplegia in 25 patients 14 of whom died, monoplegia in 6 patients, 1 of whom died, ocular palsy in 50 patients, 25 of whom died, and other cranial nerve palsies in 20 patients, 6 of whom died. The same opinion was presented by AF BJÖRKESTEN & TROUPP (1957), who reported that the mortality was not influenced by the presence of major neurological signs in connection with the bleeding. WALTON (1956) reported that out of his series of 312 patients, 53 had hemiplegia, 37 of these died, and 16 recovered. Other neurological signs were present in 131 patients, and 110 died 21 recovered. WALTON considered that the presence of neurological signs in an attack of bleeding had probably significant correlation to mortality

In the present series which mainly consists of patients that survived their first attack of bleeding, it is impossible to judge the effect of neurological signs in connection with the bleeding on mortality

The influence of neurological deficits

TABLE 16

Influence of pareses on prognosis
Aneurysm series

Patients' condition at follow up

	Number of cases	Normal working capacity	Partial disability because of: Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total	Total disability because of: Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total	Deaths and cause of death
Severe paresis on admission	9	1	1	—	—	—	—	1	1	—	—	—	—	1	1 FH 6 RH
Slight paresis on admission	3		—	—	—	—	—	—	1	—		—	—	1	1 FH 1 UD
Paresis disappeared before admission	18	3	1	1	1	3	—	5	—	—	—	—	1	1	2 FH, 6 RH, 1 UD
Total treatment or persistent paresis	30	4	2	1	1	2	—	6	2	—	—	—	1	3	4 FH, 11 RH, 2 UD
No paresis	90	20	3	—	11	1	7	22	2	—	1	1	1	5	1 FH, 37 RH, 5 UD
Total	120	21	5	1	12	3	7	29	4	—	1	1	2	8	5 FH, 48 RH, 7 UD

FH = 1st haemorrhage
RH = Recurrent haemorrhage
UD = Unrelated disease

In the aneurysm series there were 3 patients with renal diseases accompanied by high blood pressure One of the patients had polycystic kidney one chronic nephritis, and one had general amyloidosis with the kidneys affected also The two first mentioned patients died from a recurrence of haemorrhage the amyloidotic patient died of uremia.

These patients with aneurysms and coarctation of the aorta or renal diseases are very small in number but it may be assumed that the high blood pressure that is always present in such patients may lead to rupture of the aneurysm

Another concomitant disease which may be assumed to play a rôle in the prognosis of subarachnoid haemorrhage is generalized arteriosclerosis As mentioned in the chapter of etiology arteriosclerosis is considered by many authors to be a bad prognostic sign in patients with subarachnoid haemorrhage

In my no aneurysm series there were 3 patients with a diagnosis of coronary insufficiency and 1 with a diagnosis of fundus arteriosclerotica ns Three patients were partially disabled because of symptoms caused by subarachnoid haemorrhage the ophthalmological patient also had neurological defects which made him totally incapacitated Two additional patients were reported to have died of coronary infarction 3 and 5 years after their haemorrhage

In the aneurysm group there was one man with coronary insufficiency he died of cardiac infarction 5 years after the haemorrhage

The prognostic significance of arteriosclerosis of the cardiovascular system for subarachnoid haemorrhage patients is very doubtful. There is often little correlation between the frequency and intensity of the arteriosclerotic process in the different vessels of the same individual Baker et al (1961 a b) stated on the basis of 485 autopsy cases that arteriosclerosis in one organ system did not necessarily imply arteriosclerosis in another system

3 PRIMARY NEUROLOGICAL DEFICIT

In the attempt to find any signs or symptoms which would aid in estimating the prognosis of patients with subarachnoid haemorrhage the presence of neurological deficits during the attack of subarachnoid bleeding have been considered.

Hemiplegia or hemiparesis, monoplegia or monoparesis in connection with subarachnoid haemorrhage were earlier considered to be due to bleeding into the cerebral tissue. In recent years many investigators (Norlén & Olivecrona 1953 Logue 1956 and others) have shown that the cause of these neurological manifestations is in at least some of the cases severe vasospasm Spasm has also been witnessed by neurosurgeons during operation (Johnson Potter & Reid 1958). Convincing radiological evidence was provided by Ecker & Riemenschneider (1951) who illustrated the presence of vasospasm with arteriograms performed soon after subarachnoid haemorrhage and repeated several weeks later Höök & Norlén (1958) and Pribbett & Bull (1959) also demonstrated the existence of vasospasm with angiograms.

Some authors have tried to find a correlation between mortality and the presence of neurological defects during the bleeding episode Richardson & Hyland (1941) Robertson (1949) and Meadows (1951) stated that the mortality rate was somewhat greater in patients with neurological signs, in most of whom intracerebral haemorrhage was present. Hamby

(1948, 1952) on the other hand, reported that physical signs gave evidence of brain damage but were of no value in estimating the prognosis. In his series of 130 patients with subarachnoid haemorrhage there was hemiplegia in 25 patients, 14 of whom died, monoplegia in 6 patients, 1 of whom died, ocular palsy in 50 patients, 25 of whom died, and other cranial nerve palsies in 20 patients, 6 of whom died. The same opinion was presented by AF BJORKESTEN & TROUPP (1957), who reported that the mortality was not influenced by the presence of major neurological signs in connection with the bleeding. WALTON (1956) reported that out of his series of 312 patients, 53 had hemiplegia, 37 of these died, and 16 recovered. Other neurological signs were present in 131 patients, and 110 died, 21 recovered. WALTON considered that the presence of neurological signs in an attack of bleeding had probably significant correlation to mortality.

In the present series, which mainly consists of patients that survived their first attack of bleeding, it is impossible to judge the effect of neurological signs in connection with the bleeding on mortality.

The influence of neurological deficits

TABLE 16

Influence of paresis on prognosis
Aneurysm series

Patients' condition at follow up

	Number of cases	Normal working capacity	Partial disability because of: Neurological signs		Diffuse cerebral symptoms	Unrelated diseases		Total	Total disability because of: Neurological signs		Diffuse cerebral symptoms	Unrelated diseases		Total	Deaths and cause of death*)
Severe paresis on admission	9	1	1	—	—	—	—	1	1	—	—	—	—	1	1 FH 5 RH
Slight paresis on admission	3	—	—	—	—	—	—	—	1	—	—	—	—	1	1 FH 1 UD
Pareses disappeared before admission	1[illegible]	3	1	1	1	2	—	5	—	—	—	—	1	1	2 FH, 6 RH, 1 UD
Total transient or persistent pareses	30	4	2	1	1	2	—	6	2	—	—	—	1	3	4 FH, 11 RH, 2 UD
No pareses	90	20	3	—	11	1	7	22	2	—	1	1	1	5	1 FH, 37 RH, 8 UD
Total	120	24	5	1	12	3	7	28	4	—	1	1	2	8	5 FH, 48 RH, 7 UD

FH = 1st haemorrhage
RH = Recurrent haemorrhage
UD = Unrelated disease

(hemiplegia, hemiparesis) on the morbidity of the survivors is presented in Table 16 for the *aneurysm series* and in Table 17 for the no aneurysm series.

30 patients out of the total of 120 *patients with aneurysm* had pareses caused by the subarachnoid bleeding the percentage was thus 25 Since most of these patients were admitted to this hospital a considerable time *after the attack* the pareses of 18 patients had completely disappeared before admission Of the remaining 12 patients who had neurological residua on admission 5 died from *recurrences of bleeding* and 2 from sequelae of the first attack 1 died of an unrelated disease Of the 4 survivors only 1 had normal working capacity 1 was partially incapacitated due to the neurological residua 2 were totally disabled

Of the total of 30 patients that had had neurological deficits at some stage of their illness, there were 13 survivors at the time of follow up 4 of these were disabled by neurological deficits due to the haemorrhage, 1 was disabled because of neurological residua and *diffuse* cerebral symptoms.

The above analysis indicates that patients with aneurysms who survive their first attack of bleeding and who have had *neurological signs have a good chance* of recovering completely this was emphasized for example by LOGUE (1956) In this series out of 30 patients with neurological deficits 18 had recovered completely *before admission to this hospital,* and in addition one further patient later recovered enough to regain his normal working capacity This supports the theory that transient vasoconstriction is a *common cause of neurological* signs in patients with a ruptured intracranial aneurysm.

Of the 90 patients who did not have neurological deficits during their illness, 3 were found to have *epilepsy* at the follow up apparently caused by the subarachnoid bleeding; these 3 are grouped under the heading neurological signs.

Ophthalmoplegia was presented in 9 patients; *in none of them was the subarachnoid bleeding verified.* In 7 cases the angiography revealed an aneurysm on the intracranial part of the internal carotid artery in one case there were aneurysms on *both* internal carotid arteries, and in one there was an aneurysm on the anterior communicating artery Four of the patients were well and in good working condition at the follow up one was totally disabled because of epilepsy and hypertension. Three died from recurrent *bleeding* 2 months, 2 years and 8 years, respectively after the first onset of symptoms or signs from their aneurysm One patient died of an unrelated disease 8 years after the ophthalmoplegia, she was in good condition until her last illness.

In the case of 4 patients the course of the ophthalmoplegia could be followed until the point of complete recovery

In two cases the ophthalmoplegia disappeared gradually within 4 months. One patient s ophthalmoplegia had completely disappeared after a year when the patient was examined in this hospital. One patient reported after a 12 years interval that her ophthalmoplegia had disappeared completely in the meantime.

In the case of 5 patients the course of the ophthalmoplegia was not known. One was totally crippled by epilepsy and

hypertension. Four died one of thymoma, 3 of a recurrence of haemorrhage. One of these 3 patients had had her ophthalmoplegia 18 years previously: this had evidently disappeared, but she died of subarachnoid haemorrhage 18 years after the first symptom of her aneurysm.

In the no aneurysm series of 267 patients there were 65 patients (24 per cent) who had transient or persistent pareses at some stage of their illness (Table 17). The pareses of 29 patients had completely disappeared before admission. Of the 36 patients who had neurological residua on admission 3 died of an unrelated disease. Of the 33 survivors 9 had normal working capacity 7 were partially disabled because of neurological sequelae, 5 due to additional diffuse cerebral symptoms. There were 4 patients totally disabled due to neurological defects.

Of the 65 patients who had neurological signs at some stage of their illness, there were 58 survivors at the time of follow up. 20 patients had normal working capacity: 18 patients were partially or totally disabled due to neurological defects.

It is interesting to note that the frequency of hemiplegia or -paresis in patients with subarachnoid haemorrhage is

TABLE 17

I fluence of pareses on prognosis
N aneurysm series

Patients' condition t follow up

	Number of cases	Normal working capacity	Partial disability because of: Neurological signs		Diffuse cerebral symptoms	Unrelated diseases		Total	Total disability because of: Neurological signs		Diffuse cerebral symptoms	Unrelated diseases		Total	Deaths and cause of death)
Severe paresis on admission	8	—	1	1	1	—	—	3	3	—	—	1	1	5	
Slight paresis on admission	24	9	6	4	2	1	1	14	1	—	—	1	—	2	2 UD
Pareses disappeared before admission	29	11	2		8	1	1	12		—	1	1	—	2	1 FH 1 RH, 2 UD
Total	65	20	9	5	11	2	3	29	4	—	1	3	1	9	1 FH, 1 RH, 5 UD
No pareses	202	125	—	—	38	6	15	59	1	1	1	1	4	8	7 RH, 3 UD
Total	267	145	9	5	49	8	17	88	5	1	2	4	5	17	1 FH, 8 RH, 8 UD

FH = 1st haemorrhage
RH = Recurrent haemorrhage
UD = Unrelated disease

about the same in the aneurysm and the no aneurysm series 25 and 24 per cent In the no aneurysm series there were no instances of ophthalmoplegia

Also the tendency to recover after the presence of neurological deficits is about the same in both groups. In the aneurysm group 18 out of 30 recovered completely before admission and in the no aneurysm group 29 out of 65 were reported to have recovered completely from their neurological disorders.

In order to compare the condition of the patients in the aneurysm and no aneurysm series who had had pareses at some stage of their illness the figures were subjected to the chi square test and the results showed that there was no significant difference. Patients in both of the series had the same chance of recovering or suffering from neurological residua after the subarachnoid haemorrhage. The figures are very small and thus conclusions must be drawn cautiously

Summary The frequency of neurological deficits in patients with subarachnoid haemorrhage was the same for the aneurysm and the no aneurysm series. In both groups the symptoms were transient in about half of the patients

4. DISTURBANCES OF CONSCIOUSNESS

There is another sign in the clinical picture which has been considered important in evaluating the prognosis of patients with subarachnoid haemorrhage unconsciousness in association with the attack of bleeding

In MAGEE s (1943) series of 150 patients, 78 were unconscious during the attack 61 per cent of them died He concluded that unconsciousness might slightly impair the prognosis. HYLAND (1950) and MAGLADERY (1955) showed that the outlook of subarachnoid haemorrhage patients who had been unconscious during the attack was more unfavourable than that of patients who had remained conscious throughout In HAMBY s series (1948 1952) the mortality of patients who had been unconscious was twice as high as that of patients who had not lost their consciousness. WOLFE (1953) gave the same opinion JACOBSON (1954) reported that out of 141 patients who were comatose 91 died. This was 65 per cent of the patients who had coma and 26 per cent of all the 315 patients whose state of consciousness was reported He stated that the appearance of coma was indicative of a poor life prognosis. WALTON (1956) also correlated coma to mortality and found that the significance of a coma lasting 12—18 hours or more was very probable but a coma lasting not more than an hour was a less dangerous sign

In the attempt to evaluate the effect of unconsciousness on the prognosis of patients with subarachnoid haemorrhage in the present series certain facts must be kept in mind. This series consists of patients who had nearly all survived their first attack of subarachnoid bleeding The histories of the disturbances of consciousness were mostly based on reports from the hospitals where the patients had been treated during the acute stage but as the anamnestic facts in these reports were often given by the patients or their relatives, the reliability of the information about the length of

the period of unconsciousness seems questionable. In the present series a correlation between disturbances of consciousness and mortality was not possible, because the series consisted mainly of survivors. Thus the importance of consciousness or unconsciousness can be estimated only in relation to disability.

The influence of unconsciousness on the morbidity in the aneurysm and no aneurysm series is presented in Table 18.

TABLE 18

Influence of unconsciousness on prognosis

Patients condition at follow up

	Number of cases	Normal working capacity	Partial disability because of: Neurological signs		Diffuse cerebral symptoms		Unrelated diseases	Total	Total disability because of: Neurological signs		Diff. cerebral symptoms		Unrelated diseases	Total	Deaths and cause of death)
Aneurysm series															
Somnolent or unconscious few minutes	42	8	2	—	3	3	2	10	3	—	—	—	1	4	18 RH, 2 UD
Unconscious 1—24 hours	18	—	1	—	4	—	1	6	—	—	1	1	—	2	1 FH, 7 RH, 2 UD
Unconscious more than 24 hours	9		1	1	1	—	1	4	—	—	—	—	—	—	2 FH, 3 RH
Conscious	51	16	1	—	4	—	3	8	1	—	—	—	1	2	2 FH, 20 RH, 3 UD
Total	120	24	5	1	12	3	7	28	4	—	1	1	2	8	5 FH, 48 RH, 7 UD
No aneurysm series															
Somnolent or unconscious few minutes	79	11	4	2	13	4	3	26	1	1	1	—	1	4	1 FH, 4 RH, 3 UD
Unconscious 1—24 hours	32	17	2	1	7	—	3	13	—	—	—	1	1	2	
Unconscious more than 24 hours	18	7	3		3	—	—	6	1	—	—	1	1	3	2 RH
Conscious	135	78	—	2	26	4	11	43	3	—	1	2	2	8	1 RH 5 UD
Not known	2	2	—	—	—	—	—	—	—	—	—	—	—	—	1 RH
Total	267	143	9	5	49	8	17	88	5	1	2	4	5	17	1 FH, 8 RH 8 UD

FH = 1st haemorrhage RH = Recurrent haemorrhage UD = Unrelated disease

The patients were divided into four groups, three consisted of patients who had been somnolent or unconscious for *variable periods, and* one comprised patients who had remained conscious throughout

One would expect a more frequent manifestation of diffuse cerebral symptoms in patients who had been unconscious than in patients who had not experienced loss of consciousness. Table 18 shows that *in the aneurysm series* of 31 surviving patients with disturbances of consciousness 9 patients suffered from diffuse cerebral symptoms at the time of follow up 5 additional patients had similar symptoms combined with neurological signs or unrelated diseases. Out of 26 survivors whose consciousness had not been disturbed there were 4 with diffuse cerebral symptoms.

A similar analysis of *the no aneurysm series* gives the following result (Table 18) Out of the 119 surviving patients whose consciousness was disturbed for longer or shorter periods, 24 were suffering from diffuse cerebral symptoms and another 10 from combined symptoms as described above The corresponding figures were 27 and 8 respectively among 129 survivors in the »conscious» group

Summary It may be concluded that disturbances of consciousness at the time of subarachnoid bleeding are of no prognostic significance as regards cerebral symptoms in surviving patients. Their correlation to mortality cannot be evaluated on the basis of this highly selected series

A comparison between the aneurysm and no aneurysm series reveals that loss of consciousness occurred in about half of the patients in both groups; 69 out of 120 in the aneurysm series (57 per cent) and 129 out of 267 in the no aneurysm series (48 per cent) had disturbances of consciousness lasting longer or shorter periods. Statistically the difference was not significant

5 SIZE AND LOCATION OF THE ANEURYSM

a. SIZE

The correlation between the size of an aneurysm and the prognosis has been discussed in only very few reports in the literature. Large aneurysms seem to have interested investigators more particularly because of the local pressure symptoms they may cause which have sometimes led them to be mistaken for intracranial tumours (JEFFERSON 1937 and 1955, KRAUS 1952, WHITE & BALLANTINE 1961)

In their report on 113 autopsy cases of intracranial aneurysms, HOUSEPIAN & POOL (1958) considered the correlation between the size of the aneurysm and the fate of the patients and the duration of the symptoms. The size varied from 1 to 80 mm., 41 per cent were 3—5 mm. at their greatest dimension, 29 per cent were 6—10 mm., 18 per cent were 11—20 mm., and 8 per cent were over 21 mm 4 per cent had a diameter of 1—2 mm only HOUSEPIAN & POOL found that, in general large aneurysms appeared to have longer clinical histories than smaller ones, although there were several exceptions to this rule About 75 per cent of the aneurysms in each size from 1 to 40 mm ruptured, whereas only 1 out of 3 cases of aneurysm over 41 mm. ruptured The largest single group of

aneurysms causing symptoms was formed by those measuring 3—5 mm., they accounted for 21 per cent of the entire series and had a course of from 8 to 27 days from the onset of symptoms until death.

From this clinic HEISKANEN & NIEMI (1962) have published an account of 15 especially large aneurysms, these exceeded 1.5 cm on the anteroposterior or lateral diameter. The real size was calculated from the ratio between the distance of the x-ray tube and the dimensions of the aneurysm measured on the angiogram. On three patients no operation was performed. Two patients died from recurrences of haemorrhage, and one of uremia 18 months after the diagnosis was made. The prognosis of patients with large aneurysms was considered very poor in this investigation.

TABLE 19

Incidence of recurrent haemorrhage and mortality correlated to location and size of aneurysm

Location of aneurysm	Total number of cases	Large: Total number	Large: Haemorrhages	Large: Deaths	Medium: Total number	Medium: Haemorrhages	Medium: Deaths	Small: Total number	Small: Haemorrhages	Small: Deaths	Unknown: Total number	Unknown: Haemorrhages	Unknown: Deaths	Total number of patient with recurrent haemorrhages	Total number of deaths from recurrences
Internal carotid	28	4	3	2	6	5	5	18	2	2	—	—	—	11	10
Carotid bifurcation	3	3	2	2	1	1	—	—	—		—	—	—	3	2
Middle cerebral	32	3	1		12	7	6	16	6	3	1	1	1	13	9
Anterior cerebral and communicating	27	6	6	6	10	4	1	10	5	5	1	2	1	10	13
Pericallosal	3	—	—	—	2	1	1	1	1	1	—	—	—	2	2
Vertebral and basilar	4	1	1	—	1	1	1	2	2	2	—	—	—	4	3
Posterior cerebral	2			—	1	—	—	—	—	—	1	1	1	1	1
Multiple aneurysms	16										16	11	8	11	8
Total	115	16	13	10	33	19	13	47	17	14	19	14	11	53	43

In the present series the aneurysms were divided into three groups according to the size. This was estimated from the angiograms aneurysms whose *greatest* dimension was under 5 mm were classified as small, 5—10 mm aneurysms were classed as medium and those over 10 mm were classed as large Where an aneurysm was found on autopsy the size was recorded according to the autopsy report. *In 3 cases no information* about the size was given With multiple aneurysms the size was not taken into consideration because in the majority of cases the relevant aneurysm could not be diagnosed with certainty

The size of the aneurysm has been correlated *to recurrences of haemorrhage* and mortality in recurrence in Table 19 There were 16 instances of large aneurysms, recurrences occurred in 13 patients, and 10 of them died Of 33 patients with medium sized aneurysms 19 had recurrences, and 13 of them died from recurrence *Of 47 patients with small aneurysms* 17 had recurrences, and 14 of them died. Consequently the figures indicate that larger aneurysms lead to more recurrences and a higher mortality The chi square test showed that the difference between the large and the small *aneurysms* was *highly significant* in regard to the incidence of recurrent haemorrhage chi square = 9 724

As regards mortality the *difference* between large and small aneurysms was almost significant. chi square = 5 416 On the other hand the prognostic difference between neighbouring groups — between large and medium-sized aneurysms, and between medium-sized and small *aneurysms* — *could not be* statistically verified.

Summary This series and the statistical results indicate that the following conclusion is safe. Large aneurysms *rebleed* more easily and mortality in recurrent bleeding is higher in the large aneurysm group than it is in the group with small aneurysms.

b. LOCATION

The prognosis of aneurysms in different anatomical *locations* has been discussed in several papers. Most of these however only deal with problems connected with the surgical treatment of the aneurysms. Does a certain *location* make an aneurysm more threatening than others? Apart from subarachnoid haem*orrhage a ruptured intracranial* aneurysm may cause cerebral damage through bleeding into the brain tissue or provoking ischemia through strong vasospasm. The position and extent of the cerebral damage plays an important rôle in determining the symptomatology of the rupture the duration of the illness, the prospect of death and the residual incapacity of the survivors. There is not, so far any *clinical series of conservatively* treated aneurysms large enough to make a reliable prognostic analysis possible

In their monographs DANDY (1944) and HAMBY (1952) dealt with different aspects of intracranial aneurysms according to the anatomical position of the *aneurysm* on the intracranial vascular tree.

Comparatively large autopsy series were published by ROBERTSON (1949) and HOUSEPIAN & POOL (1958) in these reports the location of the aneurysm and its effect on the *prognosis* was taken into consideration. HOUSEPIAN & POOL admitted that information based on these

autopsy statistics was one-sided, but at the same time their study strongly suggested the importance of a long-term careful study of clinically verified cases.

ROBERTSON's series consisted of 93 patients, in whom 99 aneurysms were found. Massive intracerebral haemorrhage, usually reaching the ventricular system, was present in 56 cases. Ischaemic infarcts were found in 5 cases. From this analysis it can be concluded that aneurysms of the anterior cerebral and anterior communicating arteries, lying between the medial surfaces of the frontal lobes, tend to rupture into the brain substance of one or both frontal lobes. Aneurysms on the middle cerebral artery especially those lying in the Sylvian fissure between the frontal and temporal lobes, rupture into both these lobes with equal frequency. In the temporal lobe the haemorrhage may extend to the temporal horn, to the basal ganglia and to the internal capsule. None of the 6 aneurysms of the posterior communicating artery in ROBERTSON's series caused cerebral damage. The only aneurysm at the junction of the posterior cerebral and posterior communicating arteries ruptured into the temporal lobe. Of the 4 aneurysms on the posterior cerebral artery one ruptured into the thalamus, one into the temporal lobe and one into the occipital lobe.

ROBERTSON made an attempt to find a difference in the clinical course of patients with intracerebral haemorrhage and patients with subarachnoid haemorrhage alone. A considerably higher percentage of patients died during the first 24 hours than on any subsequent day and the mortality percentage was much higher for patients having only subarachnoid haemorrhage. The mortality figures for the first week showed a slight preponderance of the patients with subarachnoid haemorrhage alone. In contrast, during the second week there was a higher percentage of deaths from intracerebral haemorrhage. ROBERTSON concluded that a differentiation between groups consisting of patients with subarachnoid haemorrhage alone and patients with intracerebral haemorrhage was far from absolute. This analysis seems to indicate that the location of an aneurysm does not decisively influence the prognosis. Aneurysms which tend to rupture into the brain tissue seem to be no more dangerous than free aneurysms on the circle of Willis, which mostly cause only subarachnoid haemorrhage.

HOUSEPIAN & POOL (1958) tried to correlate the aneurysmal location and the prognosis on the basis of 85 untreated cases, which proved to have only one aneurysm each. Multiple aneurysms were excluded because it was difficult to determine the offending aneurysm.

1 Their series 28 per cent of the aneurysms were situated on the supraclinoid portion of the internal carotid artery or distal to its junction with the posterior communicating artery. 63 per cent of these aneurysms resulted in fatal haemorrhage. Aneurysms on the proximal part of the internal carotid artery accounted for 15 per cent of the entire series. 67 per cent of the patients with aneurysms in this location died from haemorrhage.

17 per cent of all the aneurysms in HOUSEPIAN & POOL's series were located on one of the middle cerebral arteries. 43 per cent of the patients died from haemorrhage from the aneurysm.

11 per cent of the aneurysms were situated on the anterior communicating artery. 73 per

cent of the patients died from rupture of the aneurysm

8 per cent of all the aneurysms were found on the junction of the anterior communicating and anterior cerebral arteries. All but one of these cases terminated with haemorrhage

All the patients with an aneurysm on the anterior cerebral artery a total of 4 per cent of all the aneurysms died as a result of rupture of the aneurysm

6 per cent of the aneurysms were found on the posterior communicating artery 86 per cent of the patients died from haemorrhage

13 per cent of the aneurysms were located in the vertebral system Fatal haemorrhage caused death in 46 per cent.

HOUSEPIAN & POOL did not draw any conclusion on the basis of the above analysis. Since the figures are small and based on an autopsy series, conclusions are certainly difficult to make although the mortality in the anterior communicating anterior cerebral artery group seems to be somewhat higher than in other groups.

Clinical studies on conservatively treated aneurysms in different locations have been made by MCKISSOCK & WALSH (1956) among others. They had 33 medically treated aneurysms on the anterior cerebral or anterior communicating artery Mortality was 92 per cent in patients belonging to MCKISSOCK's category A (patients in danger of dying in the immediate future from the haemorrhage causing admission to hospital) 39 per cent in category B (patients completely or in part recovered from the haemorrhage resulting in hospital admission seen within 8 weeks of the last bleed not in danger of dying) and none in category C (patients recovered completely or with residual signs, from the initial bleed but seen more than 8 weeks after the haemorrhage) The total mortality among these untreated patients was 51 per cent. The morbidity was not analyzed.

In MCKISSOCK & WALSH's series there were 19 cases of aneurysm on the middle cerebral artery and the mortality was 52 per cent.

The mortality among 20 patients with aneurysm on the internal carotid artery at the level of the posterior communicating artery was lower than in other locations 33 per cent. Of the 13 survivors 2 belonging to category A had only slight residual disability after 18 and 21 months respectively Among 5 patients in category B only one showed slight disability whereas the 4 others were symptom free after 1—3 years. Out of 6 patients in category C 2 showed slight disability and 4 no disability after 1—6 years.

In 15 cases of aneurysm of the internal carotid bifurcation the mortality was 47 per cent. Of the 8 survivors 3 were slightl disabled one severely disabled and the others were all well.

Two patients had aneurysms on the anterior cerebral artery distal to the anterior communicating artery and both of them died, one from the primary haemorrhage the other from a recurrence

There were 6 instances of aneurysm on the posterior cerebral artery all died and so did 3 patients with aneurysm on the basilar artery

Out of 10 medically treated patients with multiple aneurysms 50 per cent died from recurrences of haemorrhage Three survivors had minor sequelae 2 had no disability

LOGUE (1956) studied aneurysm situated on the anterior communicating and anterior cerebral arteries. Out of 73 patients 36 were treated conservatively The mortality was 44 4 per cent (16 36) One patient died from the first attack, 14 died from recurrences of haemorrhage 1 of thrombosis.

In 1960 MCKISSOCK *et al* reported the fate of 18 patients with aneurysms of the

internal carotid artery at or near the point of origin of the posterior communicating artery 20 patients died, 17 of them from recurrences of haemorrhage. Of the 28 survivors 19 were able to return to work, 6 were partially disabled and capable of light work only and 2 were totally disabled; one could not be traced.

Other authors (af Björkesten 1958, af Björkesten & Troupp 1958, 1960, Snellman *et al* 1959 Laitinen & Snellman 1960) have discussed the prognosis of aneurysms in different locations, especially comparing conservatively treated patients with surgically treated ones. As these papers deal with patients from this clinic partly included in the present series they are not reviewed.

The locations of the aneurysms in the present series are shown in Table 19 The number of patients with recurrences of haemorrhage and of those who died as a result of the recurrence are shown in the same table. It may be noted that of the 30 patients with aneurysm on the anterior cerebral — anterior communicating — pericallosal vessels 18 had recurrences of haemorrhage and 15 died from the recurrence; this is a higher incidence of recurrence than for aneurysms in other locations, apart from the few cases of aneurysm on the vertebral system. Thus aneurysms in this location seemed to be more dangerous than those situated in other locations.

However according to the statistical analysis the differences were not significant.

Summary The location of the aneurysm did not seem to influence the prognosis as regards recurrent haemorrhage or mortality The aneurysms situated on the anterior cerebral — anterior communicating — pericallosal arteries seemed to be somewhat more dangerous than those in other locations, although the difference was not statistically significant.

V RELIABILITY OF ANGIOGRAPHIC INVESTIGATION

Cerebral angiography is an invaluable method for examining patients with subarachnoid haemorrhage and the modern opinion is that it should be carried out in all cases of the condition unless there are definite contraindications (WECHSLER & GROSS 1918, FALCONER 1951 HAMBY 1952, LOGUE 1956 WALTON 1956)

It is now clear that in the majority of patients carotid angiography only visualizes that part of the cerebral vascular tree which receives its main blood supply from the carotid artery the posterior communicating and posterior cerebral arteries only fill rarely In the literature the percentage of filling has been reported as varying between 15 (LIST *et al* 1945) and 37 (TÖNNIS & SCHIEFER 1959) In order to complete the investigation vertebral angiography must be performed

In spite of every possible improvement in radiological technique details of which fall outside the scope of this investigation several cases have been reported where the arteriograms were apparently normal but where an aneurysm was revealed on operation or at the post mortem ALPERS & RYAN (1949) described two such cases, and HAMBY (1953) three. In a series of 461 patients with subarachnoid haemorrhage reported by WALSH (1956) there were 6 patients whose carotid angiograms were considered normal, though aneurysms were found at the autopsy Four of the patients had had the appropriate artery filled in the angiography but the aneurysm had not shown. Similar occurrences have been reported by FALCONER (1951) and MAGLADERY (1955)

PERRETT & BULL (1955) published a thorough investigation of the correlation between angiographic and autopsy findings. Their series consisted of angiographically investigated cases of subarachnoid haemorrhage where one or more aneurysms were found on autopsy They collected 219 cases from 1951 to 1958 9 patients were excluded because they died before vertebral angiography had been performed 187 patients had had their aneurysms accurately demonstrated radiologically The residual 23 cases (11 per cent) were studied in detail PERRETT & BULL considered that the failure to observe an aneurysm was due to 1) arterial spasm 2) observer s error 3) inadequate examination 4) observation of an intact aneurysm while the offending one was not revealed.

In 5 patients in PERRET & BULL s series spasm of the internal carotid artery and/or its branches prevented the filling of the aneurysm In 6 cases a re-assess-

ment of the angiograms showed that the aneurysm had either been misinterpreted or not seen. In four cases the arteriograms were of very poor quality. In the films of 4 patients no aneurysm could be found even after a very meticulous investigation. The sizes of these aneurysms were reported by the pathologist to be 1—2 mm. in diameter. In the case of four patients an intact aneurysm was found in the radiograms; the radiologist's attention had been focused on this aneurysm, and the bleeding one had been overlooked, although clearly visible in the angiograms.

PERRET & BULL also considered the importance of ante-mortem thrombosis of aneurysms. They emphasized that in many cases the aneurysms were still outlined by the contrast medium although a thrombus was present. They suggested that thrombosis had been previously too readily accepted as the excuse in cases of failure to visualize an aneurysm in the angiograms.

The possibility that an aneurysm might fill with a blood clot and thus not show in the angiograms was discussed by AYER (1931) among others. He described one patient who had subarachnoid haemorrhage and later died from carbon monoxide poisoning; at the post mortem examination a large completely thrombosed aneurysm was found. D… (1911) also suggested that 10—20 per cent of all ruptured aneurysms might heal in this way. Patients who had normal angiograms but in whom partially thrombosed aneurysms were later discovered have also been described by KRAYENBÜHL (1910), WECHSLER & GROSS (1918), ROBERTSON (1919), JEFFERSON (1952) and FALCONER (1951). Thrombosis of aneurysms was also reported by MAROUTH & SCHIEFER (1957), HÖÖK & NORLÉN (1958), HEMMER & UMBACH (1960) and AF BJÖRKESTEN & TROUPP (1962).

In the present series the reliability of the radiological investigation was carefully considered in the case of patients for whose haemorrhage no cause had been found angiographically. As mentioned in Chapter III, all the angiograms were re-assessed by a neuroradiologist and/or neurosurgeon with considerable experience in interpreting angiograms. In a few cases the x-ray films could not be found, and the previously written reports of the radiologists had to be considered sufficient.

Bilateral carotid angiography was performed on all the 267 patients of my own no aneurysm series. In addition, 32 of the patients also had unilateral vertebral angiography.

In evaluating the quality of the angiograms, it appeared that in 50 cases one side or both sides of the carotid angiograms could not be regarded as satisfactory in all respects: either they were imperfect technically or special projections had not been used. Most of these angiographies were performed in the early years of aneurysm surgery. Out of the 32 vertebral angiograms 8 were not regarded as technically perfect. Thus, about 20 per cent of the angiograms were in one or more respects unreliable.

Recurrences of haemorrhage occurred in 43 patients, 8 of whom died. Of the 37 patients with *non-fatal* recurrent bleeding 4 had bilateral carotid and unilateral vertebral angiography. In the case of 2 patients both posterior cerebral

TABLE 20

Incidence of recurrences and mortality correlated to completeness of angiographic investigation

	Total number of patients	Number of patients with recurrence	Number of deaths from recurrence
Complete angiography	32	4	—
Carotid angiography both posterior cerebral arteries filled	25	2	1
Carotid angiography one posterior cerebral artery filled	46	8	1
Carotid angiography no filling of posterior cerebral arteries	164	31	6
Total	267	45	8

arteries were visible in the carotid angiograms and in 8 cases one of the arteries had filled.

Vertebral angiography was not performed for any of the 8 patients who died from recurrences of haemorrhage. Both posterior cerebral arteries filled in the carotid angiograms of one patient and in the case of another patient one of them could be seen. The angiograms of two patients were considered technically poor It may be emphasized that for none of these 8 patients was the angiographic investigation complete and thus the possibility of an aneurysm cannot be excluded It is unfortunate that an autopsy was performed on only 2 of these patients, and even in these cases the result was uncertain Subarachnoid haemorrhage was confirmed in both cases, and in one of the patients the cerebral arteries were found to be atheromatous, but in neither of the autopsy cases was the bleeding point found with certainty

To correlate the completeness of the angiographic investigation and the incidence of recurrences of haemorrhage and deaths from recurrence, the patients in the present series were divided into different groups according to the degree of visualization of vessels belonging to the vertebral system. The results are shown in Table 20

In the no aneurysm series »complete» angiographic investigation — bilateral carotid and unilateral vertebral angiography — was performed on 32 patients. Four of these had a non-fatal recurrence of haemorrhage Both posterior cerebral arteries were visible in the carotid angiograms of 25 patients, two of these had recurrences, one of them ending fatally Out of 46 patients with one posterior cerebral artery filled in the carotid angiograms 8 had recurrences of bleeding, and one died Of the remaining 164 patients with no filling of the posterior cerebral arteries in the bilateral carotid angiograms, 31 had recurrences of haemorrhage and 6 of them died.

The numbers in the three first groups are small, and it is difficult to draw any conclusions, except that an aneurysm or arteriovenous malformation cannot be excluded with certainty in the patients who have been classified in this investigation as »no aneryam» patients.

An attempt was made to subject the

above figures to statistical analysis, but the results did not show any significant difference between the different groups.

The findings seem to suggest that the practical value of the vertebral angiography is limited in subarachnoid haemorrhage patients, who have survived the initial haemorrhage; a somewhat astonishing conclusion, as the incidence of aneurysms of the vertebral area according to recent investigations (SUTTON 1962) apparently is higher than previously estimated. A possible explanation would be that aneurysms of the vertebral system carry a higher primary mortality but this problem should certainly be thoroughly investigated on the basis of a larger series of completely angiographied cases.

Summary. In the no aneurysm series there was no certain difference as regards prognosis between the groups in which the posterior cerebral arteries were visualized and those where the arteries did not fill in the carotid angiograms; apparently because aneurysms of the peripheral part of the posterior cerebral artery occur comparatively rarely. On the other hand among 32 patients on whom unilateral vertebral angiography also was performed there were no deaths and only very few recurrences.

It is *concluded* that a filling of the posterior cerebral arteries in the carotid angiograms seems to be of limited practical value. An aneurysm or arteriovenous malformation cannot be excluded with certainty in the patients classified in this investigation as »no aneurysm» patients.

VI DISCUSSION

The cause of bleeding into the subarachnoid space has been the object of numerous investigations, and differing opinions have been presented in the voluminous literature published over a period of more than a hundred years. It is interesting that even in recent years the etiology of subarachnoid haemorrhage is still under discussion although better methods of investigation and increasing experience seem to have led to apparently correct conclusions. According to WALTON (1956) a ruptured arterial aneurysm is the cause of subarachnoid bleeding in about 80 per cent of cases, and an arteriovenous malformation in 10 per cent. The remaining 10 per cent of cases of which at least half is grouped under the heading »no cause found» are still under discussion In his book on arteriography SUTTON (1962) came to the conclusion that a meticulous technique will usually demonstrate an aneurysm or other causative lesion in most cases of subarachnoid haemorrhage. Where total angiography (that is, bilateral carotid and bilateral vertebral angiography) was performed the proportion of cases with positive findings in SUTTON's series rose to 97 per cent. Only in 3 per cent of cases did the investigation fail to show a cause. LOGUE too (1962) presented the opinion *that the cause of bleeding could be demonstrated in about 95—97 per cent of subarachnoid haemorrhage patients if a total angiographic investigation was performed*

The angiographic investigations have *by no means been satisfactory for all the* series of subarachnoid haemorrhage patients reviewed above. Angiographic investigations have been performed on only a fraction of the patients and only a few of the patients have been autopsied. Moreover it is apparent that in many instances the autopsy findings are not reliable because small aneurysms and minute arteriovenous malformations are difficult to detect at the autopsy if not specially looked for Thus, it is safe to assume that in most of the series published previously as well as in the present series, the angiograms and autopsies have not revealed the relevant vascular lesions — the aneurysms or arteriovenous malformations — which most probably are present in the majority of cases classified as »no cause found»

Why is the prognosis so much better for the series of patients with subarachnoid haemorrhage where no cause is found than in the aneurysm series? — in the present series ten times better If it is accepted that the cause nearly always is a small aneurysm or a minute arteriovenous malformation, it is logical to

conclude that small aneurysms bleed less: the vasospasm which has often been demonstrated to accompany a bleeding is able to close a small rupture in a minute aneurysm, and the consequences of the subarachnoid haemorrhage are thus minor. Apparently small aneurysms also have a better tendency to heal completely and never give any further symptoms. This would explain why the prognosis of patients with these is much better than that of patients whose aneurysm is large enough to be easily demonstrated in the angiograms or at the autopsy. The definitely better prognosis of small aneurysms compared to bigger ones in this series confirms these conclusions. In AF BJÖRKESTEN & TROUPP's series (1962) all the aneurysms that had bled had increased in size after the bleeding. This fact agrees with two observations made on the basis of the present series: that large aneurysms rebleed more easily and that the mortality rate increases with the number of recurrent haemorrhages.

If the cause of bleeding into the subarachnoid space is a minute arteriovenous malformation, the symptoms are often mild, because the bleeding is mainly venous, as explained by CRAIG & ADSON (1936). These malformations may be destroyed by the bleeding and give no further symptoms.

It is naturally of the utmost importance for a reliable angiographic investigation to be performed before a patient can be grouped under the heading no cause found. In the majority of the earlier studies only a small fraction of the patients had been completely investigated. In the present series only 12 per cent of the patients (32 out of 267) had had bilateral carotid angiograms and unilateral vertebral angiogram performed, the majority (235 patients) had had only bilateral carotid angiograms. None of the patients had had all four angiograms performed. Peripherally located aneurysms of the vertebral system can be visualized if the posterior cerebral arteries fill in the carotid angiograms. In the case of 71 patients of the present series one or both posterior cerebral arteries could be visualized in the carotid angiograms, but no aneurysm was seen. Technically the angiography was considered more or less unsatisfactory in about 20 per cent of the cases. Thus, there is no doubt that these investigations do not fulfil modern demands as regards angiographic standards and one has to assume that this series must contain several patients in whom an aneurysm would have been diagnosed if a complete x-ray technique had been used.

Also 8 patients in the no aneurysm series died from recurrent bleeding, one of them within 6 weeks and another within 3 months. This speaks in favour of an overlooked aneurysm.

It is natural to try to find symptoms or signs that would be of help in foreseeing the fate of patients with subarachnoid haemorrhage.

If the bleeding is a recurrent one the patients' chances of survival are much less. HAMBY (1948, 1952) stated that such a patient's chances of dying rather than living are two to one. This conclusion has been also confirmed in the present series. Judging from these results it seems a safe conclusion that in the case

VI DISCUSSION

The cause of bleeding into the subarachnoid space has been the object of numerous investigations, and differing opinions have been presented in the voluminous literature published over a period of more than a hundred years. It is interesting that even in recent years the etiology of subarachnoid haemorrhage is still under discussion, although better methods of investigation and increasing experience seem to have led to apparently correct conclusions. According to WALTON (1956) a ruptured arterial aneurysm is the cause of subarachnoid bleeding in about 80 per cent of cases, and an arteriovenous malformation in 10 per cent. The remaining 10 per cent of cases of which at least half is grouped under the heading »no cause found» are still under discussion. In his book on arteriography SUTTON (1962) came to the conclusion that a meticulous technique will usually demonstrate an aneurysm or other causative lesion in most cases of subarachnoid haemorrhage. Where total angiography (that is, bilateral carotid and bilateral vertebral angiography) was performed the proportion of cases with positive findings in SUTTON's series rose to 97 per cent. *Only in 3 per cent of cases* did the investigation fail to show a cause. LOGUE too (1962) presented the opinion that the cause of bleeding could be demonstrated in about 95—97 per cent of subarachnoid haemorrhage *patients* if a total angiographic investigation was performed.

The *angiographic* investigations have by no means been satisfactory for all the series of subarachnoid haemorrhage patients reviewed above. Angiographic investigations have been performed on only a fraction of the patients and only a few of the patients have been autopsied. Moreover it is apparent that in many instances the autopsy findings are not reliable because small aneurysms and minute arteriovenous malformations are *difficult to detect at the autopsy if not* specially looked for. Thus, it is safe to assume that in most of the series published previously as well as in the present series, the angiograms and autopsies have not revealed the relevant vascular lesions — the aneurysms or arteriovenous mal*formations — which most probably are* present in the majority of cases classified as »no cause found».

Why is the prognosis so much better for the series of patients with subarachnoid haemorrhage where no cause is found than in the aneurysm series? — in *the present series* ten times better. If it is accepted that the cause nearly always is a small aneurysm or a minute arteriovenous *malformation* it is logical to

deficits during the attack of bleeding is of no help in evaluating the prognosis as regards mortality in this highly selected series. The fact that about half of the neurological symptoms in both the aneurysm and the no aneurysm series were transient is of interest. The frequency of neurological symptoms was the same for the aneurysm and the no aneurysm series, and this fact may be considered as an evidence of the same source of bleeding in both series.

The above conclusions also apply to the disturbances of consciousness during the attack. They cannot be correlated to the mortality in recurrence in this series; disturbances of consciousness occurred during the primary attack in the case of half the patients in both series, but these patients still survived. If the disturbance of consciousness is considered a sign of the severity of the subarachnoid bleeding, this would be a noteworthy fact. On the other hand unconscious patients who survived did not suffer from cerebral symptoms more than the patients who remained conscious throughout. Thus, it seems that in this series unconsciousness during the attack had no prognostic significance

One of the reasons for conservative treatment of intracranial aneurysms in the present series was the small size of the aneurysm. This decision was apparently correct, on the basis of the present series a small aneurysm has a definitely better prognosis than has a large aneurysm.

Differences in the prognosis of aneurysms in different anatomical locations have been considered in many publications, mainly in regard to surgery; about conservatively treated aneurysms very little has been said. The present series is much too small to give any definite results in this respect, although the aneurysms on the anterior anterior communicating and pericallosal arteries seem to involve the highest mortality The dangerousness of a certain location of an aneurysm depends mainly on the adjacent structures of the brain threatened by the rupture Another possible factor is the difference in the anatomical structure of certain arteries, so that some arteries may be more apt to rupture than others. Nothing in this respect can be confirmed on the basis of the present series.

In this series 42 per cent of the patients with intracranial aneurysm died from recurrence of haemorrhage It is of interest to consider how many of these patients could have been operated upon. The main reasons for conservative treatment appear from Table 21 In the case of the majority of these patients there were several reasons; the main reason given in the patient's report has been the basis for this classification.

In 16 cases the patients died from the primary haemorrhage or a recurrence before the diagnosis was established. 13 patients were in so poor a *condition* that no angiography was performed. The angiographic investigations of two patients were not completed *before their* death. Only one patient had bilateral carotid angiography performed, no aneurysm was visualized, but one was 6 months later revealed on the posterior cerebral artery at the autopsy All these patients except the last one mentioned died soon after *admittance*

of operable aneurysm recurrent bleeding should be a strong indication to operate, because the prognosis of such patients is extremely poor

The opinion has been current that subarachnoid haemorrhage patients who survive the first haemorrhage for more than 8—12 weeks without a sign of new bleeding are more or less past the danger of recurrence In the present series even an interval exceeding 1½ years did not give much increased safety to the patients. 30 per cent of these patients suffered a further bleeding and fatalities were as frequent as they were with recurrences occurring at an earlier stage Thus, the length of the interval seems to be of little importance for the prognosis, other criteria must be taken into consideration.

The present highly selected series is of no value in considering the influence of the different factors mentioned below on the primary mortality

Age and sex did not influence the incidence of recurrent haemorrhage or the mortality in recurrence It was only in the no aneurysm series that an influence of age on the prognosis was seen older patients seemed to be more handicapped by sequelae of subarachnoid haemorrhage than younger ones. This is a logical result, seen in many other diseases the tendency to recover decreases with increasing age This was, however not apparent in the aneurysm series, probably because the number of surviving patients was so small (60)

Observations of the influence of hyper tension in the present series seem to be confusing In explanation one must first stress that the diagnosis of hypertension in the present series was more or less arbitrary Only one blood pressure recording had been made in most cases, and the diastolic pressure in particular showed so much variety that it could not be taken into consideration, although the author has been fully aware of its importance in making a diagnosis of hypertension

The results showed that patients with a blood pressure under 150 mm.Hg were more liable to have a recurrence of haemorrhage than those with a blood pressure of over 150 mm Hg On the other hand the hypertensive patient ran a greater risk of dying in the bleeding when it occurred.

It may be assumed that because of the apparently high primary mortality of hypertensive patients, only prognostically good patients survive; the reason for survival may be that the rupture is small or the aneurysm minute. Thus, because of this natural selection the prognosis of the hypertensive survivors is better as regards the chance of a recurrence of haemorrhage but once a recurrent haemorrhage occurs, it is in most instances fatal.

In the no aneurysm series the influence of hypertension on the morbidity of the surviving patients was highly significant. This is a logical result and probably correct. The number of hypertensive surviving patients in the aneurysm series (25) is apparently insufficient to give a reliable result in this respect.

The suspicion that older hypertensive people would be more handicapped by the sequelae of subarachnoid haemor rhage was not confirmed in the present series.

The presence of primary neurological

offending aneurysm could not be diagnosed with certainty 17 patients refused the suggested surgery

Out of the 96 patients who left the hospital after the diagnosis of intracranial aneurysm had been made 28 died from recurrence of haemorrhage. Some of them could probably have been operated upon and possibly saved if they had been admitted in recent years; but some of them would have succumbed in any case, either because of the surgical intervention under technically difficult circumstances, or because of the poor condition caused by the haemorrhage or other unrelated diseases.

60 patients survived up to the time of the follow up: many of these patients will certainly have recurrences of haemorrhage in the future some of them even fatal.

Despite all the progress of aneurysm surgery there will always be a certain group of patients on which surgical therapy cannot be applied for various reasons; for all these patients there is nothing but conservative treatment left with all its problems and hazards.

TABLE 21

Reasons for conservative treatment
120 patients with proven aneurysm

	Total number of cases	Fate of patients			
		Died from			Alive
		first haemorrhage	recurrence of haemorrhage	unrelated diseases	
Aneurysm considered inoperable:					
Small aneurysm	16	—	2	1	13
Technical difficulties	23	—	4	1	18
Patients admitted in 1938—1951	11	—	5	1	5
Patients died before diagnosis	16	4	12	—	—
Patients died before planned surgery	9	—	9	—	—
Poor condition of patients:					
because of haemorrhage	5	1	3	—	1
because of unrelated disease	9	—	2	3	4
Long interval since haemorrhage	2	—	—	—	2
Aneurysm overlooked	1	—	1	—	—
Multiple aneurysms	11	—	5	—	6
Patients refused suggested surgery	17	—	6	1	10
Total	120	5	48	7	60

Nine patients had an aneurysm diagnosed before their death These patients died from recurrent haemorrhage while in the hospital waiting for the operation the time interval between the diagnosis and death varying between a few hours and 10 days. Two of these patients died a matter of a few hours before the planned operation

Altogether 21 patients died in the hospital 4 of them from the primary haemorrhage

Thus 20 of the 48 patients with intracranial arterial aneurysm who died from recurrence of haemorrhage were beyond the surgery of that time: nothing could be done for them. The only possible help for some of them would have been quicker admittance to hospital, no delay in the angiographic investigations and no waiting for the surgery

The aneurysms were considered inoperable in about a third of the patients (39)· in 16 cases this was due to the small size of the aneurysm in the rest the technical difficulties were considered too great. 11 patients were admitted in the early days of aneurysm surgery (1938—1951) when an active attempt at operation was hardly ever performed in this hospital. Operation was withheld in the case of 14 patients because of their poor condition due to the subarachnoid haemorrhage or unrelated diseases. Two patients had had an interval of over one year between the haemorrhage and the diagnosis of an aneurysm, thus they were considered to be comparatively safe as regards recurrent haemorrhage. The aneurysm of one patient was discovered in the re-assessment of the angiograms, she had died of a recurrent haemorrhage in the meantime Multiple aneurysms were present in 11 patients, and the

VIII SUMMARY

This study of the prognosis of subarachnoid haemorrhage has been made on the basis of an analysis of the cases of 387 patients admitted to the Neurosurgical Clinic of the Helsinki University Central Hospital during the years 1938—1959 inclusive Intracranial arterial aneurysms were diagnosed in 120 patients; in the remaining 267 patients no cause for the bleeding was found in the bilateral carotid angiograms; 32 patients also had unilateral vertebral angiography performed. All the patients were treated conservatively All the patients but 6 had survi ed at least one episode f bleeding

At the follow up all the patients could be traced. The mean follow-up period in the aneurysm series was 5 years for the survi ors and 2 years for patients who died due to the subarachnoid haemor rhage The corresponding figures in the no aneurysm series were 1.2 and 1.5 years.

In both the aneurysm and the no aneurysm series females and males were represented in about the same proportion. In both series the highest incidence of subarachnoid haemorrhage occurred in the third and fourth decade of life th mean being just over 40 years.

Out of the 115 patients with intracranial arterial aneurysm who survived their initial attack of subarachnoid haemorrhage 63 (55 per cent) had one or more attacks of recurrent bleeding 48 patients succumbed in the recurrence, forming 42 per cent of all patients and 76 per cent of the patients wh experienced recurrence. 62 per cent of the recurrences occurred within 8 weeks from the first haemorrhage, and 41 per cent within the first 4 weeks. 30 per cent of the recurrences occurred later than 1½ years after the first haemorrhage; the longest interval was 9 years

In the no aneurysm series the incidence of recurrence of bleeding was 17 per cent (15/206)· 3 per cent died. The first recurrent bleeding occurred within 8 weeks in the case of 56 per cent, but after an interval of 1—11 years in the case of 30 per cent.

The present study shows that in a series of patients who survive their first attack of subarachnoid haemorrhage the mortality due to recurrence of bleeding is over 10 times higher among patients with proven intracranial aneurysm than among those without demonstrable vascular lesions in bilateral carotid angiograms.

45 per cent of 60 survivors in the aneu rysm series were partially or totally incapacitated due to the aneurysmal subarachnoid bleeding *The corresponding*

VII CONCLUSIONS

On the basis of the present investigation the following conclusions can be made.

1 a The mortality of subarachnoid haemorrhage patients with conservatively treated intracranial arterial aneurysms is definitely and significantly *higher than that of patients with normal* bilateral carotid angiograms. In this series the rates are 42 and 3 per cent respectively The incidence of recurrence of haemorrhage is also much higher among the aneurysm patients. The rates are 55 and 17 per cent, respectively In both series about half of the recurrences seem to occur within 8 weeks from the primary haemorrhage, but a third of the patients experience them as late as after a year or more (1—14 years)

b Also as regards the morbidity of the surviving patients, a subarachnoid haemorrhage from a *verified* aneurysm seems to be more serious than one where no aneurysm has been found the number of survivors incapacitated by the bleeding is 45 per cent in the aneurysm series as opposed to 33 per cent in the no aneurysm series.

2. a Age apparently does not influence the number of recurrent haemorrhages or the mortality in recurrence Among the patients without demonstrable vascular lesions old people seem to be more affected by the bleeding than younger ones. No differences between the two sex groups can be found as *regards mortality* in recurrence, or morbidity

b Hypertension (systolic blood pressure of over 150 mm Hg) does not seem to have any significant influence on the prognosis of patients with subarachnoid haemorrhage as regards mortality from recurrence. The hypertensive surviving patients of the no aneurysm series are more incapacitated by sequelae of their haemorrhage than the normotensive ones.

c. Neurological signs in connection with the bleeding seem to occur with the same frequency in both series; the signs are transient in about half of the patients. Loss of consciousness during the bleeding also seems to be of equally common occurrence in both series and apparently *has no significance as regards persisting cerebral symptoms in surviving* patients.

d Patients with small aneurysms (less than 5 mm in diameter) have a definitely better prognosis under conservative *treat*ment than have patients with large aneurysms. The location of the aneurysm seems to have no certain prognostic significance

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percentage in the no aneurysm series was 33

Age did not influence the number of recurrent haemorrhages or mortality in recurrence. The condition of the older age group in the no aneurysm series was more affected than that of the younger age group

There was no difference between the two sex groups as regards prognosis.

Hypertension appeared to have no significant influence on the mortality of patients with subarachnoid haemorrhage but at the time of follow up the hypertensive patients seemed to be more frequently incapacitated by sequelae persisting after their haemorrhage

The incidence of neurological deficits during the episode of bleeding was the same in the aneurysm and the no aneurysm series, 25 and 24 per cent, respectively In both groups the symptoms were transient in about half of the patients.

Loss of consciousness occurred in about half of the patients in both series. in 57 per cent in the aneurysm series and in 48 per cent in the no aneurysm series. Disturbances of consciousness at the time of haemorrhage proved to be of no prognostic significance as regards cerebral symptoms in surviving patients.

Large aneurysms bled again more easily and mortality in recurrent bleeding was higher among patients with large aneurysms than in the group with small aneurysms.

The location of the aneurysm did not seem to influence the prognosis as regards recurrent haemorrhage or mortality The aneurysms situated on the anterior cerebral — anterior communicating — pericallosal arteries seemed to be somewhat more dangerous than those in other locations, although the difference was not statistically significant

Altogether 24 patients died in the hospital, 4 of them from the primary haemorrhage, 20 from a recurrence either before the surgery which had been planned or before the diagnosis was made For various reasons 96 patients were left to be treated conservatively one died from sequelae of the first bleeding and 28 from a recurrence. Admittance to hospital at an earlier stage after the haemorrhage, no unnecessary delay in the investigations and operations, and, perhaps, a surgically more active attitude towards aneurysms formerly regarded as inoperable would probably have reduced the number of deaths to a certain degree but in this respect no exact figures can be given

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SUPPLEMENTUM 391

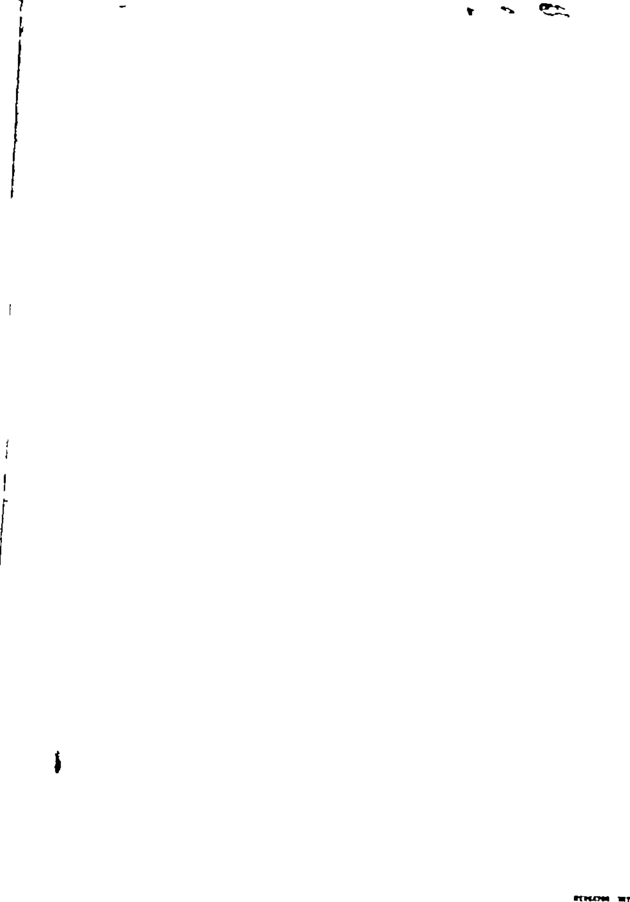
CLINICAL ANALYSIS OF 142 CASES WITH HIGH MOLECULAR WEIGHT SERUM PROTEINS

BY

W J FESSEL

Accompanies vol. 173

San Francisco, California 1962



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loma, Waldenström's disease or recurrence of carcinoma

The following two cases were equally unusual. Case 96 In a boy of 15 infective hepatitis, occurring a year previously had progressed to postnecrotic cirrhosis. Over that year petechiae, pleural and pericardial effusions, hepatic and splenic enlargements hemolytic anemia and leukopenia had developed Ultracentrifuge analysis showed: 4S 1 7 G % 7S 7 1 G % mesoglobulins 30 G { 19S, 23 G %

Case 90 A woman aged 56 had Laennec's cirrhosis a pleural effusion, hypoparathyroidism and a neurological disturbance characterized by cerebellar and midbrain lesions, posterior column involvement and peripheral neuropathy *Ultracentrifuge analysis showed* a 19S level of 45 G (6 8% of the total *proteins)*

Finally Cases 76 and 141 illustrate that a considerable degree of macroglobulinemia may be found without any apparent explanation and without its producing symptoms.

Case 76 A 70 year-old veteran was admitted to the hospital for treatment of chronic bronchitis and emphysema Three times in the past year he had had blood stained sputum to a degree consistent with chronic bronchitis. Although at one time a heavy drinker he had not drunk alcohol to excess for the past 8 years. *The physical examination showed only evidence of chronic* bronchitis and emphysema After hypergam*maglobulinemia was found* ultracentrifuge examination of the serum demonstrated that 47 5% of the serum proteins were macroglobulins (15S = 4 05 G % 22S = 0.73 G %) All tests of liver function were normal, which makes it unlikely that liver damage from alcoholism was responsible for the macroglobulinemia.

*Case 141 This 71 year-old woman was found to have a pyroglobulin during a rou*tine serological test for syphilis (which was negative) She had no symptoms or abnormal physical signs. She had had an adenocarcinoma of the uterus removed 6 years previously but there was no evidence of recurrence Ultracentrifugation of the serum *showed that 24 5 of the total proteins* were macroglobulins (15S and 26S) Microscopic examinations of the peripheral blood and bone marrow were normal, as were x rays of the bones.

CONCLUSIONS

The range of diseases in which raised levels of high molecular weight proteins are found is wide Perhaps therefore in all cases the presence of these proteins should be viewed as no more than an indicator of abnormal reticuloendothelial cell function. This could arise in several ways. Firstly abnormal reticuloendothelial cell function could be due to a hypersensitivity response, e g., to infection. This might account for the finding of macroglobulinemia in tuberculosis (Case 74) *congenital and acquired syphilis* (36 66) tropical splenomegaly (13 14) toxoplasmosis (37) and *trypanosomiasis* (16 53) The symptomatic nature *of macroglobulinemia* is clearly seen in Trypanosoma gambiense infection where, as *shown by Nicoli, Bergot* and Demarchi (53) the sometimes massive beta 2 macroglobulin elevation in the acute disease is quickly reversible by therapy Possibly the mesoglobulinemia and macroglobulinemia seen in disseminated cancer have a similar basis.

Somatic mutation is the second way in which reticuloendothelial cell function could produce abnormal proteins. This possibility as a cause of the genesis of Waldenström's disease myeloma lymphoma leukemia group

was raised by Mackay Taft and Woods (45) and Burnet (7) Burnet (7) pointed out that the type of somatic m tation which must be postulated to account for the physiological aspects f immunity grades smoothly into those concerned with the appearance of auto-immune diseases and some of the proliferative diseases of the mesenchymal cell system. Chromosomal abnormalities have been reported in both Waldenstrom s disease (42, 6 26 56) and leukemia (35) While the observ tion f such abnormalities in mam malia cells infected by herpes simplex virus (27) would equally well support the theory of an infectious etiology of these diseases, presumably physical agents may contribute to the occurrence f somatic m tation.

Another possibility which must be kept in mind is that in some instances the high molecular weight proteins may be viru par ticles. There is no evidence to support this possibility; but it might be pertinent especially in those cases of Waldenström pri mary macroglobulinemia and leukemia where proteins with a sedimentation constant as high as 39S were seen (Cases 1,2,6,33)

As to the question f specificity it must be accepted that, even in Waldenstrom disease, the ul racentrifuge findings are not pathognomonic. Equally high levels of macroglobulins were found in lymphoma and leukemia and also in the undiagnosed multisystem-disease group one patient w thout any obvious disease process (Case 141) had 24 5 % of macroglobulins and one patient with lassical Waldenström s disease had only 13 % f macroglobulins in his serum. When one considers levels of macroglobulins be tween 5 and 10% of the total serum proteins t becomes even more apparent that this find g has no diagnostic specificity But this lack f pecificity fa from lessening the alue f the bnormal ultracentrif ge find ing, should encourage the search for the func tional meaning and pathogenetic effects f these proteins. These re known, only par tially for some f the macroglobulins, e.g. thyroid antibodies, cold agglutinins, insulin antibodies, etc. (41); there is no information bout the function of mesoglobulins. When tests become ailable for a full range f functions f the high molecular weight proteins, their physical characterization in the ultracentrif ge might be either unnecessary for clinical purposes or useful only as screening procedure. Until that time the ultracentrifuge will remain valuable investigative tool.

SUMMARY

a. A clinical analysis is made f 142 cases found to have raised levels of high molecular weight serum proteins by ultracentrif gal determination.

b. The diseases found in these 142 subjects included myeloma; Waldenström disease lymphoma; leukemia; h ar disease; renal disease; connective tissue disease; eye disease sarcoidosis; chronic infection; organic and functional brain disease; multiple system disease f uncertain cause.

c. The findi gs in each group of conditions are discussed briefly and compared with other authors reports f similar cases.

d. It is concluded that the ultracentrifugal findi g of high levels of heavy serum proteins is nonspecifi and may be viewed as only reflection of reticuloendothelial cell dysfunction.

e. Because knowledge of the functions f heavy serum proteins is slight and tests for such functions are few the ultra centrif ge is still a valuable investigative tool.

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this process is uncertain (5,8,55,60,61). But there is no definite relationship between the physical properties of the abnormal proteins and their cells of origin. In myeloma the plasma cell may produce macroglobulin, as in the case reported by Motulsky, Eriksen, Volwiler and Donohue (52) and in Waldenström disease the lymphoid cell may produce mesoglobulin as was seen in cases 1, 3, 9 and 11. In myeloma, most observers have been unable to relate the morphology of the plasma cells to the electrophoretic characteristics of the proteins (28,39,58); Yaraskevas, Herrmann and Waldenström (55) recently had some success using immunoelectrophoretic fractionation. In macroglobulinemia, Kunkel (40) found that plasma cells were the only ones which stained with fluorescent macromolecular antibodies. But both Kunkel (40) and Seligmann (59) noted that in some patients who had considerable amounts of macroglobulin there were insufficient plasma cells found to account for all of the protein. Because of the scanty knowledge of their origin and function, it is concluded that the high molecular weight proteins may for the present, properly be classified solely on the basis of their sedimenting characteristics.

b) *Waldenström's Macroglobulinemia.* Among the patients with Waldenström disease were two who had had carcinoma. In Case 4 carcinoma of the floor of the mouth had been treated by radical operation four years before, and in Case 11 adenocarcinoma of the rectum five years before; in neither case was any residuum of the neoplasm found at necropsy. The relationship between carcinoma and Waldenström macroglobulinemia, an interesting one, has been noted by others. Both Kappeler, Krebs and ... (34) and Michon and Streiff (50) found about 10% of associated carcinoma in a large series of patients collected from the literature. Michon and Streiff (50) pointed to four possibilities which might account for this incidence: 1) The relationship may be a fortuitous one, considering the older age of most of these patients. 2) The macroglobulinemia may result from a secondary reticuloendothelial response to the presence of the neoplasm. 3) The abnormal protein may have a cancerogenic effect. 4) The association may be due to the known predisposition of certain individuals to multiple primary tumors. The possibility of a cancerogenic effect of macroglobulin receives no support from the two cases reported here: both had had a long interval between extirpation of the neoplasm and the appearance of the macroglobulinemia. In neither case was a recurrence of the neoplasm found at necropsy which is also against the possibility of the macroglobulinemia being caused by a reticuloendothelial response to the presence of neoplastic tissue. More evidence would be required to decide between the two remaining possibilities of a fortuitous association and of an individual's diathesis towards multiple tumors.

In case 11 the marrow contained 80% of young plasma cells, as well as increased numbers of lymphoid and lymphoid reticulum cells. There were no plasma cells in the peripheral blood. Despite the overwhelming percentage of plasma cells in the marrow the 19S level was 1.07 G.% (14.2% of the total protein) and the mesoglobulin level was 54 G.%. This patient had a bleeding tendency and slight enlargement of the spleen and lymph nodes. No skeletal lesions were seen radiologically. Therefore, the diagnosis should probably be Waldenström macroglobulinemia, although a diagnosis intermediate between it and multiple myeloma might be considered. This patient resembled quite closely the one described by Motulsky, Eriksen, Volwiler and Donohue (52) whose

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INTRODUCTION

In recent years there have been several reviews of the syndrome of primary macroglobulinemia of Waldenström and some reports have dealt with the problem of secondary or symptomatic macroglobulinemia. Most of these papers were confined to describing the clinical features f these conditions and their associated, abnormal, laboratory findings. Only few writers have considered the implications f these findings for the nosological relationships between the diseases in which they were seen (29 34 46, 50 52, 54 62a) Similarly there are very few comments in the literature about the significance, in diseases other than myelomatosis, of the finding f metoglobulins.

References 9 12, 34 44, 45 6, 48, 50, 54 63 and
** References 1 11 13 1 16, 17 29 31 36, 37 43 47 53 54 57 62a and 64.

It is the purpose of this paper to record some of the clinical data about patients found to have abnormal amounts of high molecular weight proteins in their sera, and to examine possible meanings of their presence. It is emphasized that only ultracentrif ge findings re reported here. No immunoelectrophoretic analyses were made. This may be unfortunate for tw reasons: 1) the distinction between alpha 2 and beta 2 macroglobulinemia might be especially importan in those cases with only slight elev tions f total macroglobulins; and 2) immunochemical differences between mesoglobulins might aid in diagnosis. It is clear—a point stressed further in the discussion—that multiple sorts of analyses are necessary for complete picture of the meaning of abnormal proteins.

MATERIALS AND METHODS

The ultracentrif ge measurements reported here were made by the Institute f Medical Physics, Belmont, California, 1955 61 Standard ultracentrifuge methods were used at ambient temperature (26 C) Multiple dilutions of serum were not made. Absolute concentrations were estimated by planimetric analyses of enlarged Schlieren patterns.

I this paper the term macroglobulin refers to proteins having sedimentation constant of 15S or above, usually with peak in the range of 17 21 The term mesoglobulin refers to proteins having a sedimentation constant below 15S, but above 7S, usually with peak in the range of 9-11S; some authors (60) have called these "intermediate complexes. When specific S-rates are quoted, they refer to accurately calculated rates under the ultracentrifugal conditions stated above.

A preliminary study of sera from 48 supposedly normal blood donors showed the mean level of 19S macroglobulin to be .234 grams 100ml. serum (G %) with standard deviation of .083 G. % Since 40 G.% is 2 tandard deviations beyond the mean, alues above this can reasonably be accepted as abnormal. None of the blood donors had 19S values abov 40 G % Because some uthors consider the relative value of 5% of the total serum proteins as representing an importan increase of macroglobulin, in this paper only those patients re cited whose sera had 19S alues which were above both 40 G % and 5 of the total serum proteins.

Among these 48 sera of normal blood donors were three in which mesoglobulins were detected the sedimentation constants in two of these being 10S (.35 G % 18 G.) and in the third 11S (.21 G %) This observ tion contra cts the experience of

this process is uncertain (5,8,15 40,61) But there is no definite relationship between the physical properties of the abnormal proteins and their cells of origin. In myeloma the plasma cell may produce macroglobulin, as in the case reported by Motulsky Eriksen, Volwiler and Donohue (52); and in Waldenström disease the lymphoid cell may produce mesoglobulin as was seen in cases 1 3 9 and 11 In myeloma, most observers have been unable to relate the morphology of the plasma cells to the electrophoretic characteristics of the proteins (28,59 58); Paraskevas, Heremans and Waldenström (55) recently had some success using immunoelectrophoretic fractionation. In macroglobulinemia, Kunkel (40) found that plasma cells were the only ones which stained with fluorescent macromolecular antibodies. But both Kunkel (40) and Seligmann (59) noted that in some patients who had considerable amounts of macroglobulin there were insufficient plasma cells found to account for all of the protein. Because of the scanty knowledge of their origin and function, it is concluded that the high molecular weight proteins may for the present, properly be classified solely on the basis of their sedimenting characteristics.

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others (62 64) who have stated that normal serum contains only trace amounts of proteins of this sedimenting class. It is possible that mesoglobulins may appear as a result of aggregation of 7S proteins in previously normal serum during its storage also none of these blood donors were examined physically and thus cannot be verified as healthy In this paper the mere presence of mesoglobulins is considered to be abnormal but future experience may refute this opinion.

The clinical analyses were made on three groups of subjects: 1) patients from various centers in the U.S.A. 2) psychiatric patients in the Langley Porter Institute (most of them have been reported elsewhere) 3) patients at the University of California Medical Center San Francisco. The sera used for case finding had been sent for analysis to the Institute of Medical Physics and found to contain abnormal amounts of macroglobulin or any quantity of mesoglobulin.

The primary and secondary diagnoses were taken from the patients records. Most of the psychiatric patients, but only a few of the others were examined physically by the author

FINDINGS

These are summarized in the Table. Brief clinical accounts of certain patients are included in the discussion The incidences of the various diseases have no import both because the sampling method was not random and also because the diagnostic criteria used undoubtedly differed from case to case. The large number of patients with primary psychiatric diagnoses is explained by our interest, at the Langley Porter Neuropsychiatric Institute, in the incidence and significance of macroglobulinemia in mental illness.

DISCUSSION

The main purpose of this report is to examine the sorts of diseases, in addition to primary macroglobulinemia of Waldenström and multiple myeloma, in which abnormal amounts of high molecular weight proteins were found in the serum. These were several and included the following groups lymphomas and leukemias disseminated neoplasms liver diseases and kidney diseases connective tissue diseases diabetes eye diseases diseases of uncertain cause; organic and functional brain diseases.

For convenience of discussion, each of the main groups of conditions in the Table will be considered separately Relevant features in some cases of myeloma and primary macroglobulinemia will be noted briefly but neither of these conditions will be considered at length because they have been reviewed comprehensively by others. Before discussing the clinical findings, a note on the classification of high molecular weight serum proteins seems pertinent.

a) ***Classification of high molecular weight serum proteins*** The most logical classification would be based upon the functional characteristics of the abnormal proteins, but unfortunately only a few are known. The inadequacy of a classification based rigidly upon either the physical characteristics of the proteins or their presumed cells of origin is indicated by the findings in Case 11 The marrow contained 80% of plasma cells yet the macroglobulin level was 1 07 G % and the mesoglobulin level 54 G % The plasma cell is known to produce 7S gamma globulin, mesoglobulin and macroglobulin the role of the lymphocyte in

this process is uncertain (5,8 15 40,61) But there is no definite relationship between the physical properties of the abnormal proteins and their cells of origin. In myeloma the plasma cell may produce macroglobulin, as in the case reported by Motulsky Eriksen, Volwiler and Donohue (52); and in Waldenström's disease the lymphoid cell may produce mesoglobulin as was seen in cases 1 3 9 and 11 In myeloma, most observers have been unable to relate the morphology of the plasma cells to the electrophoretic characteristics of the proteins (28,39,58); Paraskevas, Heremans and Waldenström (55) recently had some success using immunoelectrophoretic fractionation. In macroglobulinaemia, Kunkel (40) found that plasma cells wer the only ones which stained with fluorescent macromolecular antibodies. But both Kunkel (40) and Seligmann (59) noted that in some patients who had considerable amounts of macroglobulin there were insufficient plasma cells found to account for all of the protein. Because of the scanty knowledge of their origin and function, it concluded that the high molecular weight proteins may for the present, properly be classified solely on the basis of their sedimenting characteristics.

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serum showed the typical ultracentrifuge pattern of macroglobulinemia whose bone marrow was typical of myeloma and who at necropsy was found to have a plasmacellular infiltration of parenchymal organs. Cagianut (9) mentioned a patient who had clinical features and bone marrow findings of Waldenström's disease and also a plasma cell leukemia: 63.7% of the serum proteins were macroglobulins.

c) *Multiple myeloma* Several authors have considered that the transitional cases of Waldenström's disease such as those described above establish that there is no radical separation between multiple myeloma and Waldenström's macroglobulinemia Michon and Streiff (50) have classified the following forms as intermediate between typical multiple myeloma and typical Waldenström's disease: myeloma with macroglobulinemia; Waldenström's disease with abnormal gamma globulins Waldenström's disease with mesoglobulins Waldenström's disease with osteolytic lesions and Waldenström's disease with an atypical cytology The relationship of this group of disorders to the leukemias, reviewed at length by Lamy and Willk (42) is shown by the occasional case of multiple myeloma with an associated plasma cell leukemia of which two examples are cited in the Table.

Case 41 has considerable present interest because of the remarkably high level of mesoglobulins (7 5 G %) and the presence of 400 mg % of macroglobulin. The plasma cell not only produces 7S gamma globulin, as in the usual case of myeloma but also mesoglobulin and macroglobulin. Similarly macroglobulin formation is usually associated with lymphoid cells, but they may also produce mesoglobulins as in Cases 1 3 9 11 and 25

d) *Leukemia* Three patients with leukemia (Cases 33 34 and 40) had unusually high levels of macroglobulin (18 9 %; 31.2 % and 38 1%) That these are uncommon findings was shown by Fairley and Scott (19) who, among 110 patients with chronic lymphatic leukemia found only one with macroglobulinemia. Among 19 patients with chronic lymphatic leukemia studied with an immunochemical method by Miller and Karnofsky (51) none had increased macroglobulin but 8 had decreased levels. Cases 33 and 34 had chronic lymphocytic leukemia and Case 40 acute granulocytic leukemia. These cases and those of lymphosarcoma mentioned below with very high levels of macroglobulins show that the ultracentrifugal findings alone do not suffice for a diagnosis of Waldenström's disease, even when the levels of macroglobulin reach enormous proportions.

Cases 40 and 43 have unusual interest. Case 40 was a 64 year old man with acute leukemia 38 1% of his total serum proteins were macroglobulins. Despite the difficulty of identifying the precise morphological type in acute leukemia, bone marrow preparations made and read by expert hematologists at two different hospitals were considered to show acute myeloid leukemia In Case 42 a man aged 75 who complained of back pain and lassitude, splenomegaly and osteoporosis were found. At necropsy a marked myeloid hyperplasia with eosinophilia was seen in the bone marrow similar cellular elements were infiltrating the spleen liver and mesentery A careful search showed some discrete islands of plasma cells in the bone marrow Macroglobulins (19S and 27S) comprised 16 2% of the total serum proteins. There is no direct evidence that cells of the myeloid series contribute to the plasma proteins. However Fahey and Boggs (18) found that the median level of gamma globulin in 28 patients with acute myeloblastic leukemia was 140 per cent of normal about 40 per cent of the patients had gamma globulin in amounts greater than

two standard deviations from the mean nor mal alue. And Seligmann (59) saw macroglobulinemia *in a wide variety* of sarcomas of the hemopoietic system; he could not cor relate the cytological type f cell involved in the proliferation and the presence or absence of macroglobulinemia. Without other pparent source, reasonable suggestion is that in Case 40 and perhaps also in Case 42, myeloid cells might ha e been forming macroglobulins. U fortunately the patients died before an attempt could be made to extract macroglobulins from the leukemic cells in the same way as did Abrams, Cohen and Meyer (1) from lymphosarcoma tissue.

) *Lymphomas.* Various forms f lymphoma were associated with high levels of macroglobulins and most of these also had high levels of mesoglobulins. Similar obser vations were made by Jurgensons and Cooper (33) who found mesoglobulins in 2 of 3 patients w th malignant lymphoma. Azar Hill and Osserman (3) reported 13 patients with malignant lymphoma each of whose sera showed myeloma-type proteins on paper electrophoresis no ultracentrifuge data were gi en. Plasmacytosis was seen in sections of various tissues in 6 of 13; in another 4 there were reticular or lymphoid cells whose cytoplasm had trong ffinity for pyronin.

Case 23 had 77 3% Case 23 had 46.2% and Case 24 had 33 0 % of macroglobulins in their sera lymphosarcoma was diagnosed in these on the basis of one or more biopsies. The latter cases and lso Case 33 with chronic lymphocytic leukemia migh be considered to overlap W ldenstrom macroglobulinemia. In some patients it may be impossible to dif ferentiate with certainty between Walden strom macroglobulinemia and lymphomas —even using clinical, laboratory and histological evidence.

f) *Other dist ba ces f lymphatic or ticular tissue* Cases 32, 97 99 and 101 all had unusual diseases f lymphoid or reticular tissue. Case 101 had a bizarre con dition characterized by recurrent nodular lesion of the cheeks and cervical adenopathy er the prior 11 years. Biopsies f the nodule and glands both showed lymphocytic and histiocytic infiltrations with deposition of paramyloid.

The two examples of Aldrich syndrome (Cases 72 and 73) each had mesoglobulinemia and one had macroglobulinemia. In one the bone marrow showed mild lymphocytosis and both had peripheral eosinophilia. Fiv of the 7 cases of Aldrich s syndrome Krivit and Good (38) reported, had reticuloendothelial hyperplasia of the liver or spleen, or benign lymphoid hyperplasia of the lymph nodes. 5 of the patients had eosinophilia of the peripheral blood or bone marrow The multiple infections to which patients with Aldrich syndrome are liable are probably due to functional defect of the gamma globulin, which is produced in normal amounts (38) There may be similar situation in patients with lymphoma or myeloma; and t has been recorded (60) as possible congenital anomaly in child with hypergammaglobulinemia.

g) *Neoplastic diseases.* Of the several cases of neoplasm, other than lymphoma, all bu one had mesoglobulinemia, with or without macroglobulinemia, and all had multiple metastases. Possibly the abnormal proteins found in these cases of cancer reflect retic uloendothelial cell response, either immunological or irritative, to the cancer cells or their products. There is some experimental evidence that an immunological response to cancer or its products can occur (2, 35a, 67)

The alternativ hypothesis that the neoplastic cells themsel es synthesize the abnor mal proteins is supported by the demonstra tion of macroglobulins in lymphosarcoma tissue (1) and the observ tion that macroglobulinemia may subside when the lym-

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22,24,25 49). It is here noted only that abnormal proteins were found in both functional and organic psychiatric states; psychoneurotic and psychotic reactions; and i acute and chronic disorders.

l) *Miscellaneous diseases.* The several instances of abnormal proteins in association with diabetes mellitus might have resulted from either chronic infection or antibodies to insulin. Although one patient had significant level of insulin antibodies (known to be 19S molecules) the serum showed only elevation of the 10S class proteins.

Case 85 with occlusion of the central retinal artery and concomitant idiopathic glaucoma had both macroglobulinemia and mesoglobulinemia. While both these eye lesions may complicate Waldenström disease (9,34) the patient had no other clinical features of that disease and three separate studies f the bone marrow were normal.

Case 86 had bilateral tinal artery thromboses as part f cranial arteritis. The presence of abnormal serum proteins (mesoglobulin and cryofibrinogen) together with enlargement f liver and spleen and plasmacytosis f the marrow is evidence that this disease was systemic one.

The association f retinitis pigmentosa with elev tion of macroglobulins has been mentioned in a previous report (23); in 6 of 10 ser from those patients there were elev ted 19S levels (based on 19S alues from a different normal population from that reported in this paper).

m) *Diseases f uncert in diagnosis.* Most of these were multisystem diseases. The symptom complexes of these patients could not be fitted into any defined category of disease and the ailable necropsy findings were f no help. Several patients had substantial elevations of macroglobulins, which in Case 87 were as high as 60 of the total serum proteins. The following illustrations are given because current interest in the serum proteins often makes them the foci of diagnostic procedures; when they are found t be abnormal it is tempting to ascribe to them some pathogenetic significance. However perhaps the protein disturbance should be regarded as only further facet of multisystem disease in which the reticuloendothelial system is an injured, rather than the injuring, party. Yet in some patients, as in Case 87 the remarkable degree of macroglobulinemia, although unex plained on anatomical grounds, could play an important contributing role in the illness.

Case 87 An 85 year-old man seen in 1958 who complained of cough had evidence of bronchiectasis. He had had 10 years before a resection of an adenocarcinoma of the sig moid colon. The hemoglobin was 10.8 G.% W.B.C. 5,400; E.S.R. 29mm. The bone mar row on several occasions was found to be hypoplastic. In the next year the patient lost 30 pounds in weight, the liver and spleen became palpable, Bence-Jones proteinuria ppeared and total serum proteins rose to 10.4 G %. The anemia and leukopenia emained and several more bone marrow exam inations did not help diagnose the cause. In the second year after ultracentrifuge an alysis showed: 4S, 2.2 G.%; 7S, 1.4 G.%; 17S, 4.18 G.%; 24S, .96 G.%; 30S, .27 G. steroid therapy was begun. The patient became ery ill, presumably with peritonitis, was mentally confused and died several weeks later. At necropsy a severe peritonitis was found and considered to be secondary to an old rupture of the gall bladder. The lungs showed severe emphysema, lipoid pneumonia and interstitial fibrosis. There were several large renal infarcts and severe sclerosis of the glomeruli. There was no histological evidence of multiple mye

phoma is removed (57) But such findings have not been reported in epithelial neoplasms.

h) *Liver disease* Several examples of liver disease were noted mostly associated with modest elevations of macroglobulin or mesoglobulin. It is not surprising that abnormal proteins should be associated with disease of an organ having important reticuloendothelial system functions. In various liver diseases Hartmann and co-workers (29) and Heremans (30) found elevation of the beta 2 macroglobulin by immunoelectrophoresis. In some instances ultracentrifugation was made and showed macroglobulin levels of between 5 and 10 per cent of the total serum proteins. Cattan and co-workers (10) also noted increased beta 2 macroglobulin in 7 menopausal women who had a hypertrophic cirrhosis and splenomegaly of unknown etiology However there was only 3% of macroglobulin found in the single instance where analytical ultracentrifugation was made. In some of the patients liver biopsy showed a cirrhosis with an unusual degree of infiltration by lymphocytes and plasma cells.

i) *Renal disease* Case 59 with the nephrotic phase of chronic glomerulonephritis, is of considerable interest because nearly 40% of the total serum proteins of 4 2 G % were composed of high molecular weight globulins, distributed equally between mesoglobulins and macroglobulins. Hartmann and co-workers (29) believed that the kidney might play some very important role in the formation of the alpha 2 macroglobulin which was found to be elevated during the course of nephrotic syndromes of various etiologies; and although they found a patient with renal amyloidosis to have an elevation of the alpha 2 macroglobulin, it was not seen in a patient with amyloidosis localized to the liver Yet very few patients reported in the Table had a serious, coincidental renal lesion.

j) *Connective tissue diseases.* This group of diseases is well known to be associated with the presence of abnormal serum proteins. Only two cases will be singled out for discussion

Case 61 was that of a man aged 56 with rheumatoid arthritis in the so-called malignant phase, with widespread cutaneous ulcerations. Rheumatoid factor (which is 19S protein) was present in very high titer (1 56 000 by the tanned cell method) Yet the 19S level as measured in the ultracentrifuge was normal the 9S level was 91 G % It is quite common to find as here, a considerable degree of rheumatoid factor activity but normal 19S levels, a combination also illustrated by Case 64 This 56 year old woman had clinical evidence of chronic thyroiditis, an active arthritis of the rheumatoid type and an alcoholic cirrhosis. The serum contained very high levels of rheumatoid factor (1:448 000) and of thyroglobulin antibodies (1:112 000 by the tanned cell method) Nucleoprotein antibodies were present in a titer of 1 256 (nucleoprotein latex method) and the LE cell preparation was strongly positive. The rheumatoid factors and most thyroglobulin antibodies are macroglobulins. The beta 2 macroglobulin was increased as shown by immunoelectrophoresis, yet the ultracentrifuge analysis showed normal 19S levels (23 G %) the 11S level was 46 G % These two cases demonstrate again the inadequacy of a classification based only upon the physical characteristics of the protein molecules.

k) *Central nervous system diseases and psychiatric disturbances* The number of patients with psychiatric disturbances listed (Table) is disproportionately large because of our special interest in this problem. Some possible meanings of the presence of these abnormal proteins in psychiatric diseases have been discussed at length (20,21

was raised by Mackay Taft and Woods (45) and Burnet (7) Burnet (7) pointed out that the type of somatic mutation which must be postulated to account for the physiological aspects of immunity grades smoothly into those concerned w th the ppearance of auto-immune diseases and some f the proliferativ diseases of the mesenchymal cell ystem. Chromosomal bnormalities have been reported in both Waldenström disease (4a, 6, 26, 56) and leukemia (35) While the observ tion f such abnormalities in mammalian cells infected by herpes simplex virus (27) would equally well support the theory of an infectious etiology of these diseases, presumably physical agents may contribute to the occurrence of somatic mutation.

Another possibility which must be kept in mind is that in some instances the high molecular weight proteins may be irus particles. There is no evidence to support this possibility but t might be pertinent especially in those cases of Waldenstrom pri mary macroglobulinemia and leukemia where proteins with sedimentation constant as high as 39S were seen (Cases 1,2 6,33)

As to the question of specificity t must be accepted that, en in W ldenström disease, the ultracentrifuge findings are not pathognomonic. Equally high levels of macroglobulins were found in lymphoma and leukemia and also in the undiagnosed-multisystem-disease group; one patient without any obvious disease process (Case 141) had 24 5 % of macroglobulins and one patient with classical Waldenström disease had only 13% of macroglobulins in his serum. When one considers levels of macroglobulins be tween 5 and 10% of the total serum proteins it becomes even more pparent that this find ing has no diagnostic specificity But this lack f specificity far from lessening the alue f the abnormal ultracentrifuge finding, should encour ge the search for the func tional meaning and pathogenetic effects of these proteins. These are known, only par tially for some f the macroglobulins, e.g. thyroid antibodies, cold aggl tinins, insulin antibodies, etc. (41); there is no information about the function of mesoglobulins. When tests become ailable for full range of functions of the high molecular weight proteins, their physical characterization in the ultracentrifuge might be either unnecessary for clinical purposes or useful only as screening procedure. Until that time the ultracentrifuge will remain a aluable in estigative tool.

SUMMARY

a. A linical analysis is made f 142 cases found to ha raised levels of high molecular weigh serum proteins by ultracentrifugal determination.

b. The diseases found in these 142 subjects included myeloma; Waldenstrom disease; lymphoma; leukemia; li er disease; renal disease; connective tissue disease eye disease sarcoidosis; chronic infection organic and functional brain disease; mul tiple ystem disease of uncertain cause.

c. The findings in each group of conditions are discussed briefly and compared with other uthors reports of similar cases.

d. It is concluded that the ultracentrif gal finding of high levels of heavy serum proteins is nonspecific and may be viewed as only reflection f reticuloendothelial cell dysfunction.

e. Because knowledge of the f nctions f heavy serum proteins is slight and tests for such functions are few the ultracentrif ge is still a valuable in estigativ tool.

loma Waldenström's disease or recurrence of carcinoma.

The following two cases were equally unusual. Case 96 In a boy of 15 infective hepatitis, occurring a year previously had progressed to postnecrotic cirrhosis. Over that year petechiae pleural and pericardial effusions, hepatic and splenic enlargements hemolytic anemia and leukopenia had developed Ultracentrifuge analysis showed: 4S 1 7 G % 7S, 7 1 G %; mesoglobulins, 30 G % 19S 23 G %

Case 90 A woman aged 56 had Laennec's cirrhosis, a pleural effusion hypoparathyroidism and a neurological disturbance characterized by cerebellar and midbrain lesions, posterior column involvement and peripheral neuropathy Ultracentrifuge analysis showed a 19S level of 45 G % (6 8 % of the total proteins)

Finally Cases 76 and 141 illustrate that a considerable degree of macroglobulinemia may be found without any apparent explanation and without its producing symptoms.

Case 76 A 70 year-old veteran was admitted to the hospital for treatment of chronic bronchitis and emphysema. Three times in the past year he had had blood stained sputum to a degree consistent with chronic bronchitis. Although at one time a heavy drinker he had not drunk alcohol to excess for the past 8 years. The physical examination showed only evidence of chronic bronchitis and emphysema After hypergammaglobulinemia was found ultracentrifuge examination of the serum demonstrated that 47 5 % of the serum proteins were macroglobulins (15S = 4 05 G % 22S = 0.73 G %) All tests of liver function were normal, which makes it unlikely that liver damage from alcoholism was responsible for the macroglobulinemia

Case 141 This 71 year-old woman was found to have a pyroglobulin during a routine serological test for syphilis (which was negative) She had no symptoms or abnormal physical signs. She had had an adenocarcinoma of the uterus removed 6 years previously but there was no evidence of recurrence. Ultracentrifugation of the serum showed that 24 5 % of the total proteins were macroglobulins (15S and 26S) Microscopic examinations of the peripheral blood and bone marrow were normal, as were x rays of the bones.

CONCLUSIONS

The range of diseases in which raised levels of high molecular weight proteins are found is wide. Perhaps therefore in all cases the presence of these proteins should be viewed as no more than an indicator of abnormal reticuloendothelial cell function. This could arise in several ways. Firstly abnormal reticuloendothelial cell function could be due to a hypersensitivity response, e.g., to infection This might account for the finding of macroglobulinemia in tuberculosis (Case 74) congenital and acquired syphilis (36 66) tropical splenomegaly (13 14) toxoplasmosis (37) and trypanosomiasis (16 53) The symptomatic nature of macroglobulinemia is clearly seen in Trypanosoma gambiense infection where, as shown by Nicoli Bergot and Demarchi (53) the sometimes massive beta 2 macroglobulin elevation in the acute disease is quickly reversible by therapy Possibly the mesoglobulinemia and macroglobulinemia seen in disseminated cancer have a similar basis.

Somatic mutation is the second way in which reticuloendothelial cell function could produce abnormal proteins. This possibility as a cause of the genesis of Waldenström's disease myeloma lymphoma leukemia group

was raised by Mackay Taft and Woods (45) and Burnet (7) Burnet (7) pointed out that the type of somatic mutation which must be postulated to account for the physiological aspects of immunity grades smoothly into those concerned with the appearance of auto-imm ne diseases and some of the proliferati e diseases f the mesenchymal cell system Chromosomal abnormalities ha been reported in both Waldenström's disease (4a, 6 26 56) and leukemia (35) While the observation of such abnormalities in mammalian cells infected by herpes simplex virus (27) would equally well support the theory of an infectious etiology f these diseases, presumably physical gents may contribute to the occurrence f somatic mutation.

Another possibility which must be kept in mind is that in some instances the high molecular weight proteins may be virus pa ticles. There is no evidence to support this possibility but t might be pertinent espe cially in those cases of Waldenstrom primary macroglobulinemia and leukemia where proteins with sedimentation constant as high as 39S were seen (Cases 1,2,6,33)

As to the question of specificity t must be accepted that, even in Waldenström disease, the ultracentrif ge findings are not pathognomonic. Equally high levels of macroglobulins were found in lymphoma and leukemia and also in the undiagnosed-multi system-disease group one patient without any obvious disease process (Case 141) had 24 5 % of macroglobulins and one patient with classical Waldenström's disease had only 13 f macroglobulins in his serum. When one considers levels of macroglobulins between 5 and 10% of the total serum proteins it becomes even more apparent that this finding has no diagnostic specificity But this lack f specificity far from lessening the alue f the bnormal ultracentrif ge finding, should encour ge the search for the func tional meaning and pathogenetic effects f these proteins. These are known, only par tially for some of the macroglobulins, e.g. thyroid antibodies, cold gglutinins, insulin antibodies, etc. (41); there is no information about the function of mesoglobulins. When tests become ailable for full range f functions of the high molecular weight proteins, their physical characterization in the ultracentrif ge might be either unnecessary for clinical purposes or useful only as screening procedure. U til that time the ultracentrifuge will remain a valuable in estigati tool.

SUMMARY

a. A clinical analysis is made f 142 cases found to ha raised levels of high molec ular weight serum proteins by ultracen trif gal determination.

b. The diseases found in these 142 subjects included myeloma Waldenstrom disease; lymphoma; leukemia; liver disease; renal disease; connective tissue disease eye disease sarcoidosis; chronic infection organic and f nc ional brain disease; mul tiple system disease of uncertain cause.

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						cells, was prompted by unresponsiveness of anemia to iron therapy
9	M47	95 = 1 11	155 = 1 07) 218 = (9/(18 2%)	Waldenstrom macroglobulinemia.		Past history of syphilis and recurrent gonorrhea. Frei test positive. Alkaline phosphatase 23 units. Serum bilirubin—3 3 mg %. Marrow typical plasmacytes and lymphocytes.
10	M74		1 0 (14 5%)	Probable Waldenstrom disease	Carcinoma of prostate. Pneumoconiosis.	Bloody pleural effusion. Pericarditis. Aortic insufficiency. Pruritus. Marrow and lymph nodes suggestive of Waldenström's disease, with lymphocytic infiltration.
11	M71	54	1 07 (14 2%)	Waldenstrom macroglobulinemia.	Rectal carcinoma 5 years ago.	No evidence of recurrence of carcinoma. Marrow 40% plasma cells.
12	F67		1 27 (12 7%)	Waldenstrom macroglobulinemia.	Cirrhosis of unknown cause	
13	F	85 = 3 9 105 = 1 0 118 = 0 5		Multiple myeloma.		Marrow cells between typical myeloma cell and lymphocyte.
14	M	85 = 4 7 128 = 36		Multiple myeloma.	Senile emphysema	
15	M	95 = 3 82 115 = 58		Multiple myeloma.		
16	M62	95 = 2 1		Multiple myeloma.	Chronic alcoholism.	
17	F57	96		Multiple myeloma.		
18	M72	58		Multiple myeloma	A[illegible] teomy [illegible] Chronic pyelonephritis. Generalized arteriosclerosis.	Past history of treated syphilis.

Case	Sex and Age	Values in G% or (in brackets) % of total serum proteins: Mesoglobulins	Macroglobulins	Major Diagnosis	Other Diagnosis	Comments
1	F	10S = 32	15S = 7 05 21S = 1 31 26S = 63 30S = 15 (63 7%)	Waldenström's macroglobulinemia		
2	M68		19S = 6 03 25S = 1 58 30S = 67 (60 1%)	Waldenström macroglobulinemia.	Arteriosclerotic cardiovascular disease.	
3	M	27	10 8 (48 5%)	Waldenström macroglobulinemia.		Peripheral neuropathy for years before other manifestations. Amyloidosis. Hemolytic anemia.
4	M67		15S = 3 78 22S = 84 28S = 37 (48 0%)	Waldenström macroglobulinemia	Healed rheumatic valvulitis. Carcinoma of floor of mouth 4 years ago.	Carcinoma treated by radical surgery no evidence of recurrence at autopsy W B C. = 56,000-76% prelymphocytes, 2% blasts and 20% neutrophils.
5	M45		16S = 3 9 22S = 69 27S = 18 (43 1%)	Intermediate between Waldenström macroglobulinemia and multiple myeloma		Marrow: increased plasma cells. Lymph nodes loss of architecture and massive infiltration by plasmacytoid and plasma cells. Muscle dense infiltration by plasma cells marked resemblance to plasmacytoma.
6	M49		17S = 1 9 23S = 34 32S = 07 (27 0%)	Waldenström's macroglobulinemia.		
7	M85		1 55 (23 3%)	Waldenström macroglobulinemia.		
8	M61		16S = 1 72 24S = 20 (21 9%)	Waldenström macroglobulinemia.	Bleeding duodenal ulcer	No enlargement of lymph glands or spleen. Marrow examination, which showed typical plasma

							W.B.C. = 9,350, 21% monocytes.
31	λ152	40			Hodgkin's disease.		
32	λ150			40 (3.9%)	Reticulo-endotheliosis		Case published in ref. 4
33	λ158			168 = 4.7 225 = 1.1 255 = 48 335 = 29 395 = 14 (58.9%)	Chronic lymphocytic leukemia		Antibody to "o". High titer of cold agglutinins.
34	λ161			195 = 2.6 255 = 11 (11.3%)	Chronic lymphocytic leukemia, bl k m phase		
35	Γ			1.0 (16.7%)	Chronic lymphocytic leukemia.		
36	λ176	37			Chronic lymphocytic leukemia.	Diabetes mellitus. Several basal cell carcinomas removed from cheeks.	
37	F40			56 (6.7%)	Acute myelomonocytic leukemia.	Chronic pneumonitis. Chronic thyroiditis.	
38	F37	42			Acute myelomonocytic leukemia		
39	λ176	19			Acute myelomonocytic leukemia		
40	λ164			2.45 (38.1%)	Acute granulocytic leukemia.		Cold agglutinin titer >1:160. Auto- and iso-hemagglutinins.
41	λ173	7.3		40 (5.2%)	Acute plasma cell leukemia.	Arteriosclerotic cardiovascular disease. Bronchopneumonia.	Radiolucent areas in skull and two recently fractured ribs.
42	λ174			195 = 1.37 275 = 12 (16.2%)	Chronic myeloproliferative syndrome		Marked myeloid hyperplasia with eosinophilia and some plasmacytosis of marrow. Infiltration of liver, spleen and G.I. tract with same cells as in marrow

Case	Sex and Age	Values in G% or in brackets % of total serum proteins		Major Diagnosis	Other Diagnosis	Comments
		Monoglobulins	Macroglobulins			
19	F52	9S = 52		Multiple myeloma with plasma cell leukemia		
20	F75	49		Multiple myeloma		Latex fixation test for rheumatoid factor = 1 1280
21	F58	46		Multiple myeloma.		Past history of multiple severe allergies.
22	F54	23		Multiple myeloma	Acute disseminated coccidioidomycosis. Cyst of IIIrd ventricle.	
23	F		16S = 8 52, 22S = 1 72, 28S = 68 (77 3%)	Lymphocytic lymphosarcoma.		
23			18S = 2 53, 26S = 73, 33S = 26 (46 2%)	Lymphosarcoma		
24	F		1 03 (13 0%)	Lymphosarcoma		
25	M	10S = 40	94 (15 3%)	Lymphosarcoma		
26	F73		47 (5 4%)	Lymphosarcoma	Thyroidectomy for asymptomatic goiter	
27	M24		55 (7 4%)	Hodgkin disease		
28	M11	9S = 46	68 (7 2%)	Hodgkin disease		
29	M20	9S = 62	47 (5 7%)	Hodgkin disease, generalized.		B.S.P. = 20%
30	F59	53		Hodgkin disease, paragranuloma	Diffuse non-toxic goiter	Coombs neg in hemolytic anemia. Cold agglutinin titer 1 40

31	λ152	90		Hodgkin disease.		W.B.C. = 9,350, 21% monocytes.
32	λ180		40 (5 9%)	Reticulo-endotheliosis.		Case published in ref. 4
33	λ158		165 = 4 7; 228 = 1 1; 265 = 48; 338 = 29; 398 = 14 (58 9%)	Chronic lymphocytic leukemia.		Antibody to High titer of cold agglutinins.
34	λ161		198 = 2 6; 255 = 11 (31 2%)	Chronic lymphocytic leukemia bl k phase		
35	I		1 0 (1(7%)	Chronic l mphocytic leukemia.		
36	λ176	37		Chronic lymphocytic leukemia.	Diabetes mellitus. Several basal cell carcinomas removed from cheeks.	
37	F40		56 (6 7%)	Acute m lomonocytic leukemia	Chronic pneumonitis. Chronic thyroiditis.	
38	Γ37	42		Acu my lomonocytic leukemia		
39	λ176	39		Acut my lomonocytic leukemia.		
40	λ164		2 46 (38 1%)	Acute granulocytic leukemia.		Cold agglutinin titer >1 160. Auto- and iso-hemagglutinins.
41	λ173	7 5	40 (3 2%)	Acute plasma cell leukemia.	Arteriosclerotic cardiovascular disease. Bronchopneumonia.	Radiolucen reas in skull and t recently fractured ribs.
42	λ175		195 = 1 37; 278 = 12 (16 2%)	Chronic myeloproliferat syndrome		Marked myeloid hyperplasia with eosinophilia nd some plasmacytosis of marrow. Infiltr tion of liver spleen and G.I. tract with same cells as in marrow.

Case	Sex and Age	Values in G% or (in brackets) % of total serum proteins		Major Diagnosis	Other Diagnoses	Comments
		Macroglobulins	Macroglobulins			
43	M60	11S = 39	16S = 2 38 22S = 54 27S = 20 (31 8%)	Disseminated carcinoma primary site uncertain.		Metastases apparently of pancreatic origin no primary neoplasm in pancreas. Marrow normal.
44	F80	98	1 05 (12 6%)	Sarcoma of bone.		
45	F25	33	66 (6 9%)	Choriocarcinoma.		Metastases to lung, bladder and possibly liver
46	M68		44 (6 1%)	Reticulum cell sarcoma of femur		Liver involvement (B.S.P = 17%) Multiple bony metastases. Carcinomatous myoneuropathy with clinical picture resembling myotrophic lateral sclerosis.
47	M	9S = 1 98 11S = 1 0 13S = 1 08		Adenocarcinoma of bladder		
48	M60	1 54		Carcinoma of breast.		Generalized carcinomatosis.
49	F56	72		Ovarian papillary cyst adenocarcinoma.		Multiple metastases.
50	M61	58		Carcinomatous lymphangitis of lung from unknown primary		Adenocarcinoma of stomach resected 5 years previously
51	M55	42		Carcinoma of kidney		Metastases to lung and brain. Marrow plasmacytosis. Peripheral monocytosis (17%)
52	M29	41		Carcinoma of colon.		Multiple metastases.

53	F48	39		Carcinomatosis from unknown primary		Multiple metastases.
54	M23	35		Carcinoma of testis.		
55	M		59 (8.1%)	Post-necrotic cirrhosis.		
56	M70	37	66 (7.4%)	Chronic liver disease unknown etiology	Chronic brain syndrome. Arteriosclerotic heart disease.	
57	M		49 (5.3%)	Alcoholic cirrhosis.		
58	M	44		Post-necrotic cirrhosis.	Old gastrectomy and iron deficiency anemia.	
59	M57	83	83 (19.7%)	Chronic membranous glomerulonephritis with nephrotic syndrome.		Biopsy limited to kidneys.
60	M61	44		Chronic glomerulonephritis.		Marrow slight increase of plasma cells.
61	M56	91		Rheumatoid arthritis.	Chronic pyelonephritis. Renal calculi.	Severe arteritis. FII titer >1:56,000.
62	I	46		Rheumatoid arthritis and purpura.		Marrow 37% lymphocytes.
63	M27		56 (11.5%)	Probable systemic lupus erythematosus.		Chronic glomerulonephritis. Purpura after exposure to cold. One positive L.E. cell preparation.
64	F56	46		Probable systemic lupus erythematosus.	Alcoholic cirrhosis. Chronic thyroiditis. Active arthritis.	FII 1:448,000. Lupus factor 1:256. Lupus cells present. Thyroid antibodies 1:112,000.
65	M	98 – 23		Polyarteritis nodosa.		Multiple system involvement. Extensive involvement of mucosa of mouth, nose, throat. Also involved were: kidneys; bladder; bowels; pancreas; skeletal muscles; pericardium.

Case	Sex and Age	Values in G% or (in brackets) % of total serum proteins: Macroglobulins	Values in G% or (in brackets) % of total serum proteins: Macroglobulins	Major Diagnosis	Other Diagnosis	Comments
66	F	25	56 (8 1%)	Probable dermatomyositis.		Severe arteritis.
67	F42		48 (5 2%)	Probable derm tomyositis.		Cryoglobulinemia.
68	F60	98 = 3 04 13S = 52	16S = 74 (6 9%)	Sjögren s syndrome.		Biopsy of parotid extensi e infiltr tion by pla m cells. Thrombocytopenia. Marrow normal.
69	F	1 51		Sjögren syndrome.		Pigmentation and tenderness of legs. W B C. 3,950. L.E. cell p eparation negative. Marrow hypercellular no increase in plasma cells or small lymphocytes.
70	F45	43		Sjögren syndrome.	Chronic cystic mastitis.	
71	M19		19S = 52 (5 2%)	Connectiv tissue disease f ndiagnosed type.		Severe Raynaud' phenomenon muscle and joint stiffness. Hepatosplenomeg ly generalized adenopathy Marrow plasmacytosis. B.S.P = 12%. Urine Bence Jones protein; red cells white cells granula casts.
72	M 11 mos.	40		Aldrich syndrome.		Marrow: lymphocytosis thrombopenia. W.B C. 16,200 (16% eosinophils)
73	M5	16	52 (5 9%)	Aldrich syndrome.	Rheum toid arthritis.	W B.C. persistent eosinophilia (p to 18%)
74	M77		82 (14 1%)	Act t berculous.	Chronic thyroidit s.	T berculous lesions found i apex of l ng mediasti l gl nds nd

						splenomegaly. Anaplastic carcinoma found in one mediastinal gland primary tumor not found.
75	127		44 (5 5%)	Acute sarcoidosis.		Disease of 2 months d ration. Marrow β ll d hyper plasia with increase in eosinophils and monocytes.
76	M170		155 = 4 05 / 225 = 73 (47 5%)	Chronic bronchitis and emphysema.	Chronic alcoholism until 8 years ago.	B.S.P. = 3½%. Thymol turbidity zero. Marrow slight increase in lymphocytes and plasma cells.
77	M67	51		Bronchiectasis.	Severe infection by E coli.	
78	M174	40		Pulmonary embolism and pulmonary edema.	Coronary artery disease.	
79	F	HS = 26	165 = 3 22 / 238 = 72 / 285 = 29 (39 2%)	Diabetes mellitus.	Uterine fibroid.	Renal disease. Old cataract extraction.
80	146		52 (7 2%)	Diabetes mellitus.		Diabetic retinopathy. Diabetic neuropathy. Chronic pyelonephritis.
81	149	48		Diabetes mellitus.		Diabetic retinopathy. Diabetic neuropathy. Peripheral vascular disease. Renal disease. Insulin antibodies present.
82	M123		44 (5 3%)	Guillain-Barré syndrome.		
83	M119		44 (5 3%)	Brain stem encephalitis.		
84	M		57 (7 5%)	Retinitis pigmentosa.		
85	M172	40	41 (5 3%)	Occlusion of central retinal artery (R). Idiopathic open angle glaucoma (R).	Nephrolithiasis.	

Case	Sex and Age	Values in G% (or in brackets) % of total serum proteins		Major Diagnosis	Other Diagnosis	Comments
		Microglobulins	Macroglobulins			
86	F72	35		Cranial arteritis with bilateral retinal artery thrombosis.		Temporal artery pulsations absent biopsy showed lymphocytic infiltrate and one giant cell. Liver and spleen palpable. Marrow: slight plasmacytosis. Plasma fibrinogen 1 17G%. Cryofibrinogen 07G%.
87	M187		17S = 4 18; 24S = 96; 30S = 27 (60 0%)	Multisystem disease of certain cause.	Bronchiectasis. Carcinoma of sigmoid colon 12 years ago.	Hepatosplenomegaly Anemia leukopenia, elevated E.S.R. Bence-Jones protein na. Several bone marrow examinations normal. Autopsy no evidence of recurrence of cancer; perforation of gall bladder; chronic pyelonephritis; interstitial fibrosis of lung
88	F	9S = 42	17S = 2 44; 23S = 83; 29S = 34 (35 3%)	Multisystem disease of uncertain cause.		Paresthesiae of fingers and toes. No abnormal physical signs. Marrow hypoplastic but contained 10% plasma cells.
89	M152		64 (8 8%)	Multisystem disease of uncertain cause.		Recurrent petechiae. Malabsorption syndrome. Mild anemia. Marrow normal.
90	F56		45 (6 8%)	Multisystem disease of uncertain cause.		Pleural effusion. Laennec's cirrhosis. Hypopituitarism Bizarre neurological picture with cerebellar disturbance midbrain lesion, posterior column lesion; peripheral neuropathy

91	A185	41	54 (6 2%)	Multisystem disease of uncertain cause		Capillary fragility and cutaneous purpura. Hepatosplenomegaly. Renal lesion, with proteinuria, hematuria and casts.
92	161		41 (5 7%)	Multisystem disease of uncertain cause	Adenocarcinoma of ary	H p tosplenom g ly. A toxic hemolytic anemia. Thrombocytopenia. Plasmacytosis in both peripheral blood (26%) and bone marrow. Bilateral renal cortical necrosis.
93	F53	49	46 (5 1%)	Multisystem disease of uncertain cause.		Arteriosclerotic cardiovascular disease. Hypothyroidism. Cirrhosis. Splenomegaly. Neurologic picture resembling myotrophic later l sclerosis.
94	A363	63		Multisystem disease of uncertain ca se.	Glaucoma. Congenital L h, dronephrosis.	Dizzy spells, epistaxis, diarrhea and arth algia. Hepatomegaly, Anemia. E.S.R. 125. Normal bone marrow
95	A1	98 → 34		Multisystem disease of uncertain cause.		Intermittent claudication without gross peripheral vascular disease. General malaise. W.B.C. 10,600 to 16,450 on one occasion 6% lymphoblasts and on another 10% eosinophils. Marrow: slight increase of eosinophils.
96	A115	30		Multisystem disease of ncertain cause.		Pleural effusion; pericardial effusion; mitral valvulitis; hepatosplenomegaly; postnecrotic cirrhosis; p t kl s hemolytic anemia, leukopenia.
97	F67		163 = 1 2 } 253 = 09 } (15 8%)	Undiagnosed disease.		Fever and widespread lymphatic hyperplasia. Lymph node biopsy showed reactive hyperplasia

Case	Sex and Age	Values in G% or (in brackets) % of total serum proteins: Macroglobulins		Major Diagnosis	Other Diagnosis	Comments
		Macroglobulins	Macroglobulins			
98	F39	95 – 65	41 (5 7%)	Undiagnosed disease.		Petechiae on legs for 3 years. Peripheral blood and bone marrow normal.
99	M	95 – 42	55 (6 9%)	Undiagnosed disease.		Enlargement of lymph nodes and spleen for 2 years. Blood counts, urinalyses and marrow examinations normal. *Lymph node biopsy* severe reactive hyperplasia.
100	F	105 – 46	46 (4 8%)	Undiagnosed disease.		Purpura and ulcerations of legs.
101	F57	105 – 29		Undiagnosed disease.		Purplish-brown nodules on face with cervical adenopathy; recurrent over 10 years. Lymph node biopsy variously interpreted as lymphosarcoma or lymphogranuloma. W B C. = 4,500. Marrow: normal.
102	M		63 (7 0%)	Sociopathic personality disturbance, sexual deviation (homosexuality)		D.S.I < 1%.
103	M		62 (6 0%)	Sociopathic personality disturbance, with drug addiction.		
104	F15		50 (5 9%)	Emotionally unstable personality		
105	F41		42 (3 5%)	Hysterical personality with psychophysiological muscular skeletal reaction.		Mother and sister both psychotic.

106	M		42 (5 3%)	Sociopathic personality disturbance with sexual deviation (homosexuality)		
107	M		46 (5 3%)	Personality trait disturbance emotionally unstable personality		
108	M		50 (5 2%)	Passive-aggressive personality [illegible] type.		
109	M		48 (5 5%)	Sociopathic personality disturbance: sexual deviation (homosexuality).	Recent thyroidectomy	
110	F38		46 (5 8%)	Depressive reaction, mild, situational.		
111	M17		46 (5 3%)	Adjustment reaction of adolescence.		
112	M		44 (5 3%)	Personality trait disturbance. Emotionally unstable personality with compulsive trends.		B.S.P. < 1%
113	F23		41 (5 1%)	Emotionally unstable personality		
114	M		46 (5 1%)	Personality trait disturbance, passive-aggressive personality		
115	M		46 (5 1%)	Sociopathic personality disturbance, dyssocial reaction.	Probable C.N.S. lues.	B.S.P. < 1%

Case	Sex and Age	Values in Q% or (in brackets) % of total serum proteins		Major Diagnosis	Other Diagnosis	Comments
		Mesoglobulins	Macroglobulins			
116	F32		53 (7 5%)	Schizophrenic re tio paranoid		Recurrent myocarditis of unknown cause, 5 years ago. Occasional leukopenia (<5000) Marrow normal. B S.P <5%
117	M54		55 (6 4%)	Schizophrenic r tio paranoid.		
118	F		48 (5 8%)	Schizophrenic reactio catatonic.		
119	M		48 (6 1%)	Schizophrenic rea t on paranoid.	C.N.S lues.	Has peripheral lymphocytosis.
120	F22		54 (6 0%)	Schizophre ic r t o acut nd fferentiated.		
121	F29		53 (6 0%)	Schizophrenic r t on acute nd ff rentiated.		
122	F38		50 (5 8%)	Schizoph enic re tio schizo-affective		E.S.R = 31 m.m.
123	M		50 (5 6%)	Schizoph enic re ti chronic nd ff enti ated.		
124	M		47 (5 6%)	Schizophrenic r t schizo-affective.		
125	M15		4((5 4%)	Schizopl ren t o catatonic.		
126	M21		45 (5 5%)	Schizophrenic t chronic d ff nt ted		Psych tric disturbance in both parents.

127	116	21	90 (5 1%)	Schizophrenic re ctio acute undifferentiated.		Sister had thrombocytopenic purpura.
128	A155	40	41 (4 9%)	Schizophrenic re ion schizo-affectiv	Rheumatoid arthritis. Chronic inactive pulmonary T.B.	
129	A174	28	40 (5 0%)	I vol ion l psychosis, melancholia.		
130	A151	53		M l -d pres de-pressed.	Rheumatic heart disease.	
131	A159	21		M -depressi de-pressed		
132	151		51 (6 4%)	Chronic brain syndrome with epilepsy	Multiple congenital skeletal deformities	
133	A1		57 (6 2%)	Chronic brain syndrome associated with tra ma		
134	F73	47	57 (6 2%)	Senile brain disease b psychosis		
135	A162	25	48 (5 7%)	Chronic brain syndrome ith psychosis		
136	A159	32	40 (4 5%)	Korsakoff psychosis.		
137	A1	44		Chronic brain syndrome, alcoholism.		
138	F48	22	36	Chronic brain syndrome, soc ted wi h bi-frontal m l gl m and psychosis.		
139	A163	46		Chronic brain syndrome associated with neoplasm (hrom phobe adenoma)		

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IV Ornithine carbamyl transferase activity in human tissue homogenates. *J Lab. clin. Med* 56. 218—221 1960.

V Serum ornithine transcarbamylase activity in normal individuals. *Enzymol. biol clin 1* 47—60, 1961

VI Chloroform anaesthesia in obstetrics. Its effect on the serum activity of ornithine carbamyl transferase, glutamic oxalacetic transaminase, and glutamic pyruvic transaminase *Acta obst gynec Scand* 39 661—674, 1960. In collaboration with N Wiqvist and S. Yllner.

VII. Increased biliary pressure and serum ornithine carbamoyl transferase activity in man. An experimental study *Enzymol biol clin 1* 159—169 1962. In collaboration with G Jonson and L Norrsell.

VIII. Determination of serum ornithine carbamoyl transferase activity A highly specific test for liver and biliary tract disease Observations in 695 patients. *Acta med Scand 172.* 1962. *In press*

References to these papers will be made by the numerals I—VIII

INTRODUCTION

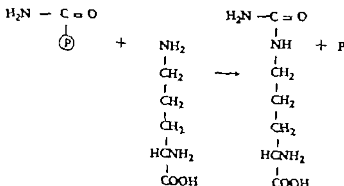
In 1956 P. Reichard purified the enzyme ornithine carbamoyl transferase* from rat liver[21]. The enzyme was shown to be identical with citrulline phosphorylase first discovered by Krebs and associates[13]. As these workers pointed out, this enzyme occurs in mammals only in the liver. On the suggestion of P. Reichard and together with him a method for measuring small amounts of ornithine carbamoyl transferase in serum was worked out (I). The method was applied to explore whether the determination of the serum activity of ornithine carbamoyl transferase might be of use in the diagnosis of liver diseases in man. It was considered possible that the activity of OCT in serum (S-OCT) might be elevated in cases of liver disease just as the activity of glutamic oxalacetic transaminase has been shown to be in cases of myocardial infarction[16].

The investigation was started in 1956; preliminary results were presented the same year at the Annual Meeting of the Swedish Medical Society and further results were published subsequently (I—VIII). The aim of this thesis is to summarize the essential points of these individual studies and to discuss their significance.

METHOD

It was demonstrated by Krebs & Henseleit[14] in 1932 that liver slices formed urea from carbon dioxide and ammonia. These authors formulated the now familiar urea cycle, which consists essentially in the intermediate formation of ornithine, citrulline and arginine. Citrulline has later been shown to be formed by the following reaction[6, 11]

(1) Carbamoyl phosphate + ornithine ⟶ citrulline + phosphate



Abbreviations

OCT ornithine carbamoyl transferase — GPT glutamic pyruvic transaminase
GOT glutamic oxalacetic transaminase — AP alkaline phosphatase

Serum samples may be stored at +4° C for one week or at −15° C for more than one year without apparent decrease in their enzyme activity. Whole blood may be stored for at least one day at room temperature. Addition of heparin, citrate or oxalate or slight haemolysis does not affect the enzyme activity (I). Observations have shown that repeated thawing and freezing lowers the S-OCT level in an unpredictable manner.

The isotope technique was used in all the studies reported in papers II—VIII. With each series of sera a "control" of known S-OCT activity was incubated. For sera analysed in May 1958 and again in October 1960 the S-OCT was unchanged. The mean S-OCT activities of normal subjects collected in 1956—7, 1958 and 1960 were the same. When, in late 1961* multiple S-OCT determinations on 3 sera were performed by the isotope and micro-diffusion methods, the relationship between the two methods was found to be the same as in 1957. Hence, it is reasonable to conclude that S-OCT analyses performed during these 4 years are quite comparable.

Most other workers on S-OCT have used the micro-diffusion method, and have expressed their results in μg of nitrogen per 0.5 or 1.0 ml of serum. To facilitate comparison of the results obtained by the two methods the regression line was calculated for the activities recorded for slightly more than 100 sera (V). The relation between the quantity of nitrogen (y) expressed in μg, and the quantity of $^{14}CO_2$ (x) in 0.5 ml of serum, expressed in μmoles, is given by the equation $y = 27.2x + 0.57$.

STUDIES ON THE DOG

OCT content of various organs (II). — OCT determinations performed on homogenates of organs showed the liver to contain extremely large quantities of the enzyme (corresponding to 5800 μmoles of $^{14}CO_2$ per g of wet tissue). The amounts for the small intestine and duodenum were 1.5 per cent of the liver values (calculated per unit weight), while the other organs and body fluids contained small or negligible amounts.

Elimination of OCT from the blood stream (II). — OCT administered intravenously in the form of liver homogenate was eliminated rapidly from the blood stream. After 24 hours the activity in serum had fallen by 80 per cent. The same rate of decrease was observed in the convalescent stage following liver damage induced by means of carbon tetrachloride.

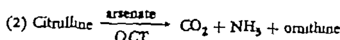
S-OCT in liver cell damage (II). — A peak activity of 1000 times the initial value was recorded 2 days after administration of carbon tetrachloride to induce liver damage. The 2 surviving animals showed normalization of S-OCT in 14 days.

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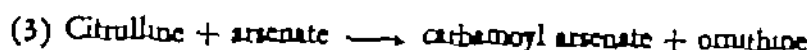
The enzyme catalyzing this reaction is carbamoyl phosphate *L*-ornithine carbamoyl transferase[22] (trivial name ornithine carbamoyl transferase*)

In the presence of arsenate, ornithine carbamoyl transferase catalyzes the breakdown of citrulline

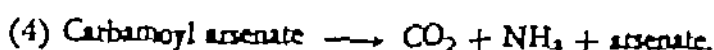


$$(2)\ \text{Citrulline} \xrightarrow[OCT]{\text{arsenate}} CO_2 + NH_3 + \text{ornithine}$$

This reaction may be considered to consist of the following two stages



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Reaction (3) is the reverse of reaction (1) but with arsenate replacing the phosphate. *Reaction* (4) represents the instantaneous non-enzymatic break-down of the unstable carbamoyl arsenate.

As reaction ( ) shows, a measure of the activity of OCT is provided by the formation of CO_2 or of NH_3 resulting from the arsenolysis of citrulline Accordingly two methods have been worked out for the determination of S-OCT one of them involving the estimation of *labelled CO* from citrulline carbamoyl ^{14}C, and the other the estimation of NH_3 *from non-labelled* citrulline by a microdiffusion technique (I) The S-OCT activity measured by the isotope method is expressed in micromoles of $^{14}CO_2$ formed by 0 5 ml of serum in 24 hours under standard conditions, while in the microdiffusion method the activity is expressed in micromoles of NH_3 formed by 0 5 ml of serum in 24 hours under standard conditions. A close correlation between the two methods has been demonstrated (I) No stoichiometric formation of $^{14}CO_2$ and NH_3 was obtained, however as different substrate concentrations were employed in the two methods.

It was found that high concentrations of both arsenate and citrulline were necessary for optimal S-OCT activity similar results with the liver enzyme were first described by Krebs *et al* [13] A similar parallel was found in respect of the pH optimum and the temperature stability of the enzyme activity Furthermore, it was noted that on paper electrophoresis S-OCT activity showed an electrophoretic mobility at pH 8 6 similar to that of purified liver OCT The relationship between the OCT levels observed for 101 sera was identical for the isotope and microdiffusion methods (I)

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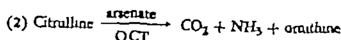
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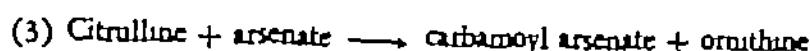
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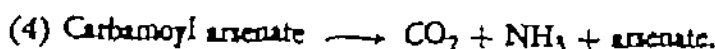


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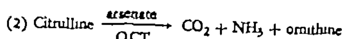
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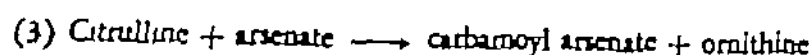
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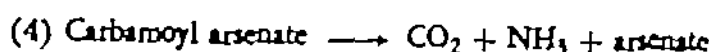


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The mean S-OCT and the variance for the subjects below 26 years of age was smaller than for the older class. No sex difference was evident. The frequency distribution was asymmetrical. The logarithms of the S-OCT values had a for practical purposes normal distribution.

There was no diurnal variation in S-OCT nor was the level affected by vigorous exercise or by a single dose of alcohol.

S-OCT after chloroform anaesthesia (VI) — S-OCT S-GOT and S-GPT were examined in primigravidae before, during and after deli ery Towards the end of the second stage of labour one-half of the patients received a maximum of 10 g of chloroform dripped on an open gauze mask (by the routine method used at the Karolinska Hospital) while the other half constituted a control group.

In the chloroform group the S-OCT increased to reach peak value 3 days after anaesthesia statistically the difference from the control group was highly significant. Significant differences were also recorded after 3 days for S-GOT but not for S-GPT These findings suggest the following conclusions.

( ) Chloroform dministered in doses not exceeding 10 g dripped on an open gauze mask may affect the liver and produce an increase in S-OCT and S-GOT

(ii) An increase in S-OCT is more sensitive indicator of the acute affect of chloroform on the liver than is an increase in S-GOT or S-GPT

S-OCT in experimentally increased pressure in the biliary tract (VIII) — The pressure in the biliary tract was increased by administering morphine. Of a group of 10 cholecystectomized subjects on whom the study was performed 6 developed biliary pains in 5 of these an increase in S-OCT was observed the maximum of 60 times the original value was recorded 5—7 hours after the injection, and 12 hours later the level was still high The S-GOT and S-GPT were elevated in 3 and 2 subjects, respectively· the rises began later than for S-OCT and peak value of 6 times the initial value was noted 7 hours after the injection. The S-AP increased only in one patient and then not to pathologic value For 2 patients the S-OCT determination was the only one of the tests to show definite elevations

It would appear from these results that an increase in S-OCT is considerably more sensitive index of biliary stasis of short duration than are the corresponding increases in S-GOT S-GPT and S-AP

S-OCT case f arious d eases (VIII) — The S-OCT activity was determined for some 3000 blood specimens from 695 patients Elevated levels were observed frequently for cases of li er and biliary tract conditions and other diseases with liver damage as a complication, for instance cancer metastases in the liver, chronic alcoholism and failure of the hepatic circulation (heart decompensation or tachycardia with fall in blood pressure)

A greater number of cases of liver disease or affected liver ga e pathologic values of S-OCT than of S-GOT S-GPT or S-AP

S OCT on ligation of the common bile duct (II) — The S-OCT activity increased to a maximum of 500 to 1000 times the initial value in 4 days. Ten days later the enzyme level had fallen to 100 times the initial value in spite of the biliary stasis.

S-OCT on partial obstruction of the common bile duct (III) — Preliminary experiments[8] on partial biliary stasis have shown that the S-OCT increases rapidly following ligation. The experiments were continued on 3 cholecystectomized dogs with external biliary fistulas by a method worked out by G Jonson[12] whereby a regulated constant pressure can be produced in the biliary tract of unanaesthetized dogs. The fistula pressure, the abdominal pressure and the bile secretion rate were recorded continuously and blood samples were taken hourly for analysis The dogs were fed once daily and with each meal the bile output of the previous 24 hours was given, mixed in the food.

It was found to be of major importance whether or not the dogs had been fed prior to the experiments. A secretion pressure that did not give rise to an increase in enzyme activity in plasma in the fasting dog produced marked elevations after the dog had taken food and bile. The OCT activity in plasma began to increase at a lower secretion pressure than did the AP activity or bilirubin concentration. At a very high pressure all the parameters showed increases When the plasma AP increased by 0 1 Buch-Buch unit the OCT increased by about 0 017 μmoles of $^{14}CO_2$ Thus there was a more than tenfold greater rise in OCT than AP in relation to the initial level When the secretion pressure was increased by one centimetre of water in the range 15—22 cm the rise in OCT activity in plasma was intensified by about 0 020 μmoles per hour

STUDIES ON MAN

OCT content of various organs (IV) — The activity in homogenates of human organs showed extremely high values for the liver (corresponding to 2500 μmoles of $^{14}CO_2$ per g of wet weight) For the small intestine and duodenum the quantities were about 14 per cent of the liver value The corresponding figures for the colon and stomach were 0 2 per cent. For the lungs, spleen and bladder bile still lower OCT activities were recorded — about 0 05 per cent of that of the liver The heart muscle, brain, blood cells, hepatic bile kidney striated muscle and the bone marrow had values that were less than 0 005 per cent of that of the liver The level in the blood serum was about 0 001 per cent.

S-OCT in 222 normal subjects (V) — The study was performed on a group of apparently healthy persons employed at the hospital and a number of apparently healthy men selected at random.

Comparison of the latter group with the former showed that as regards the S-OCT activity the whole series was probably representative of the normal population.

the case for S-AP activity in serum it is thus necessary to know the distribution of the enzymes in the various organs, the manner in which they are liberated from cells into the blood and the rate at which they disappear from the blood stream.

A high S-GPT activity is a more specific sign of liver damage than a high S-GOT[27, 28]. This is explained by the fact that GPT is located mainly in the liver and only to a minor extent in the kidney heart and skeletal muscle, whereas GOT is present in almost all organs, although the highest concentrations are found in the liver, heart and skeletal muscle[29].

OCT distribution — The observation by Krebs *et al* [13] in 1955 of OCT activity only in the liver suggested that an elevated S-OCT level might be a specific sign of liver damage. The present investigation was undertaken to examine this possibility. A check of earlier observations on the amounts of OCT in the various organs revealed a similar distribution in man (IV) the dog (II) and the mouse[15]. Extremely high activities were observed in the liver, and much smaller amounts in the small intestine; only traces were present in the other organs. The failure of earlier investigators to detect OCT in other organs than the liver may have been due to a lower sensitivity of their method[15].

Thus, OCT was found to be more specifically localized in the liver than are GOT or GPT and clinical observations also indicated that an elevation of the S-OCT activity is more specific sign of liver damage than an elevation of S-GOT or S-GPT (VIII).

Liberation and elimination of the enzyme — It has been shown that other intracellular enzymes such as GOT[2,23] may be liberated from necrotic cells into the blood stream. A similar behaviour may be assumed in respect of OCT. It would, however, seem unlikely that all the elevations of S-OCT observed in experiments on the animals and human subjects (III, VI, VII) including the patients (VIII) were due solely to cell necrosis. Several investigators have demonstrated by *in vitro* experiments that transaminases[10] and aldolase[29] may be liberated from apparently vital cells to the surrounding medium. Moreover, it has been shown *in vivo* that the S-GOT level is increased by induced fever[9] or physical exercise[25]. These observations suggest that OCT, too, may be liberated not only from necrotic but also from vital cells.

The elimination of S-OCT was extremely rapid in dogs with toxic hepatitis (II) and in patients in the icteric stage of epidemic hepatitis (VIII). Elevated S-OCT levels diminished in dogs with the common bile duct ligated (II) and were normalized in patients with permanent occlusion of the duct (VIII). Since S-OCT disappears from the serum during biliary stasis and severe liver damage, elevations of S-OCT activity would probably be due to an increase in the liberation of the enzyme from liver cells rather than to reduced elimination from serum.

Normal S-OCT — A skew distribution of the S-OCT for normal subjects similar to that observed in this study (V) has been reported by Demange *et al* [4]. These investigators, however, did not find a lower mean S-OCT level in persons below 26 years than for the older subjects. As their method (a modification of the microdiffusion technique) was

Increased S-OCT was found, however not only among patients with definite liver and biliary tract conditions, but also among cases of myocardial disease (without decompensation) rheumatoid arthritis, acute enteritis, systemic lupus erythematosus and allied collagen conditions. The elevated S-OCT in these cases, many of which also displayed increased S-GPT was probably due to an increase in the leakage of OCT from the liver cells. In cases of acute enteritis the possibility of such a leakage from the cells of the small intestine into the blood serum cannot be ruled out, however

DISCUSSION

Of the two methods for measuring OCT activity in serum, the isotope technique involving measurement of labelled CO_2 showed the more consistent results with smaller errors of analysis.

The large dispersion of values noted for the micro-diffusion method especially when the S-OCT activity was low may account for the conclusion reached by Novak[20] and Seidler *et al* [26] that the level of S-OCT is an insensitive indicator of liver damage Despite its lower accuracy the microdiffusion method has been more widely used in clinical work[1, 3, 5, 17, 20, 24, 26] in all probability because no isotope substrate or equipment for isotope measurement is required.

The numerical results obtained by the isotope method are to a large extent dependent on the ^{14}C labelling of the substrate and the sensitivity of the equipment for isotope measurement. Instead of controlling these two factors separately the sum of them was measured by relating the OCT levels obtained to values for sera kept for several years as standards. It was shown that calculated in this way the mean S-OCT for normal subjects was constant from 1956 to 1960 Furthermore the relation between the values obtained by the isotope and the microdiffusion methods was constant over the same period Hence, a certain S-OCT value obtained at any time during the investigation represents the same enzyme activity

It is invariably difficult to prove the identity of enzymes from different sources. The serum OCT in the present study bore a close similarity to highly purified OCT from rat liver High concentrations of citrulline and arsenate were necessary for optimal enzyme activity and the pH and temperature stability curves were similar The electrophoretic mobilities of the OCT from the two sources were almost the same As no other citrulline splitting enzymes are known, these facts strongly indicate that the measured activity is due to ornithine carbamoyl transferase

The enzymes most frequently determined for the purpose of liver diagnosis are GOT GPT and AP An elevated activity of these enzymes in serum is due either to an increase in the amount liberated from damaged cells, as seems to be the case for GOT and GPT[27] or to reduced metabolism or excretion — by the liver for instance — as is thought to be

the case for S-AP activity in serum t is thus necessary to know the distribution of the enzymes in the various organs, the manner in which they are liberated from cells into the blood and the rate at which they disappear from the blood stream.

A high S-GPT activity is a more specific sign of liver damage than a high S-GOT[27, 28]. This is explained by the fact that GPT is located mainly in the liver and only to a minor extent in the kidney heart and skeletal muscle, whereas GOT is present in almost all organs, although the highest concentrations are found in the liver heart and skeletal muscle[28].

OCT distribution. — The observation by Krebs *et al* [13] in 1955 of OCT activity only in the liver suggested that an elevated S-OCT level might be a specific sign of li er damage. The present investigation was undertaken to examine this possibility A check of earlier observations on the amounts of OCT in the various organs revealed a similar distribution in man (IV) the dog (II) and the mouse[15]. Extremely high activities were observed in the liver and much smaller amounts in the small intestine only traces were present in the other organs. The failure of earlier investigators to detect OCT in other organs than the liver may have been due to   lower sensitivity of their method[13].

Thus, OCT was found to be more specifically localized in the liver than are GOT or GPT and clinical observations also indicated that an elevation of the S-OCT activity is a more specific sign of liver damage than an elevation of S-GOT or S-GPT (VIII).

Liberation and elimination f the enzymes. — It has been shown that other intracellular enzymes such as GOT[2, 23] may be liberated from necrotic cells into the blood stream. A similar behaviour may be assumed in respect of OCT It would, however, seem unlikely that all the elevations of S-OCT observed in experiments on the animals and human subjects (III, VI VII) including the patients (VIII) were due solely to cell necrosis. Several investigators ha e demonstrated by *in vitro* experiments that transaminases[10] and aldolase[29] may be liberated from apparently ital cells to the surrounding medium. Moreover it has been shown *in   ivo* that the S-GOT level is increased by induced fever[9] or physical exercise[25]. These observations suggest that OCT too, may be liberated not only from necrotic but also from ital cells.

The limination of S-OCT was extremely rapid in dogs with toxic hepatitis (II) and in patients in the icteric stage of epidemic hepatitis (VIII) Elevated S-OCT levels diminished in dogs with the common bile duct ligated (II) and were normalized in patients with permanent occlusion of the duct (VIII). Since S-OCT disappears from the serum during biliary stasis and severe liver damage, elevations of S-OCT activity would probably be due to an increase in the liberation of the enzyme from liver cells rather than to reduced elimination from serum

Normal S-OCT. — A skew distribution of the S-OCT for normal subjects similar to that observed in this study (V) has been reported by Detrange *et al* [4]. These investigators, however did not find a lower mean S-OCT level in persons below 26 years than for the older subjects. As their method (modification of the microdiffusion technique) was

Increased S-OCT was found, however not only among patients with definite liver and biliary tract conditions, but also among cases of myocardial disease (without decompensation) rheumatoid arthritis, acute enteritis, systemic lupus erythematosus and allied collagen conditions. The elevated S-OCT in these cases, many of which also displayed increased S-GPT was probably due to an increase in the leakage of OCT from the liver cells. In cases of acute enteritis the possibility of such a leakage from the cells of the small intestine into the blood serum cannot be ruled out, however

DISCUSSION

Of the two methods for measuring OCT activity in serum, the isotope technique involving measurement of labelled CO_2 showed the more consistent results with smaller errors of analysis.

The large dispersion of values noted for the micro-diffusion method especially when the S-OCT activity was low may account for the conclusion reached by Novak[20] and Seidler *et al*[26] that the level of S-OCT is an insensitive indicator of liver damage Despite its lower accuracy the microdiffusion method has been more widely used in clinical work[1, 3 5 17 20, 24, 26] in all probability because no isotope substrate or equipment for isotope measurement is required

The numerical results obtained by the isotope method are to a large extent dependent on the ^{14}C labelling of the substrate and the sensitivity of the equipment for isotope measurement. Instead of controlling these two factors separately the sum of them was measured by relating the OCT levels obtained to values for sera kept for several years as standards It was shown that, calculated in this way the mean S-OCT for normal subjects was constant from 1956 to 1960 Furthermore, the relation between the values obtained by the isotope and the microdiffusion methods was constant over the same period Hence, a certain S-OCT value obtained at any time during the investigation represents the same enzyme activity

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The enzymes most frequently determined for the purpose of liver diagnosis are GOT GPT and AP An elevated activity of these enzymes in serum is due either to an increase in the amount liberated from damaged cells, as seems to be the case for GOT and GPT[27] or to reduced metabolism or excretion — by the li er for instance — as is thought to be

hepatic circulation or to secondary liver damage of any other origin. The liver was the probable site of abnormal leakage of OCT into the blood stream, although in cases of acute enteritis, damage to the cells of the small intestine may have been responsible for the elevated S-OCT values.

Concluding remarks — If a simple method for measuring S-OCT activity having the *same sensitivity and reproducibility as the isotope method could be devised this test* would be more widely used in clinical work. Because of its *specificity* for the liver this test might prove of value in the diagnosis of liver and biliary tract conditions. The high *sensitivity* of the method might be of great value in cases of biliary stasis of short duration, such as passage of stones or biliary tract dyskinesia, and in cases of mild damage to the liver. The problem of sub-clinical liver damage and its importance in the development of cirrhosis might be approached from a new angle; moreover, any toxic action of drugs on the liver might be detected earlier.

probably less sensitive than the isotope technique used in the present investigation, small differences may not have been detectable, especially in view of the relatively small number of subjects composing their series

S-OCT in biliary stasis — An increase in the pressure in the biliary tree is probably a common feature of disorders such as biliary dyskinesia and biliary calculus. Since these temporary elevations of biliary pressure are sometimes accompanied by normal S-GOT S-GPT and S-AP activities, more sensitive tests are required Experiments on the dog have shown that moderate and temporary rises in biliary pressure are reflected in increases in S-OCT that in relation to the initial values are at least ten times greater than the increases in S-AP (III) Experiments on human subjects gave similar results (VIII) An increase in S-OCT following a temporary rise in biliary pressure was greater and was recorded in more subjects, than was the case for S-AP S-GOT or S-GPT The determination of S-OCT activity may therefore prove of value in distinguishing between abdominal pains due to, or accompanied by elevations in biliary pressure and abdominal pains of other origin.

S OCT in liver damage — In cases of extensive damage to the liver a diagnosis of liver disease will almost invariably be possible on the basis of the history the physical examination and a few simple liver tests. Where the damage is slight, however the liver disease may remain undetected owing to the atypical symptoms and the low sensitivity of the liver tests employed A more sensitive test of liver cell damage is then required.

In women receiving obstetric chloroform anaesthesia the S-OCT was more often elevated, and to a greater extent, than the S-GOT and S-GPT (VI) In cases of liver cirrhosis, carcinoma of the liver and hepatic damage due to alcoholism or severe heart decompensation, the S-OCT more often gave pathologic values than the other liver tests compared (VIII) These observations also suggest that the S-OCT activity is a more sensitive index of acute liver-cell damage than the S-GOT and S-GPT activities.

Another advantage of the S-OCT determination is the high liver specificity of this enzyme, as illustrated by the fact that in cases of myocardial infarction the S-OCT activity was normal while the S-GOT was elevated, and that in a case of muscle damage (dermatomyositis) normal S-OCT was associated with elevated S-GPT (VIII)

On the other hand, the S-OCT determination is seldom of value in the differential diagnosis of jaundice Extremely high S-OCT values are seen in early cases of biliary stasis and infectious hepatitis (VIII) Moderately elevated and even normal S-OCT values are occasionally recorded after longstanding biliary stasis and in cases of liver cirrhosis accompanied by jaundice (VIII)

S-OCT in patients without known liver disease — Normal S-OCT levels were recorded in most cases of diseases and conditions other than those of the liver and biliary tract, although an elevated level was found in some cases of rheumatoid arthritis, systemic lupus disseminatus, myocardial infarction and acute enteritis. These increases may possibly be due to liver involvement as a component of the disease itself to mild disturbances of the

hepatic circulation or to secondary liver damage of any other origin. The liver was the probable site of abnormal leakage of OCT into the blood stream, although in cases of acute enteritis, damage to the cells of the small intestine may have been responsible for the elevated S-OCT values.

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SUMMARY

1 Ornithine carbamoyl transferase (OCT) is a mammalian liver enzyme involved in the urea cycle

2 Two methods for the quantitative estimation of OCT have been developed, one involving measurement of $^{14}CO_2$ formed from citrulline carbamoyl ^{14}C, and the other, the estimation of NH_3 formed from unlabelled citrulline by a microdiffusion technique The former technique also enables accurate determinations to be made of the normal OCT activity in serum

3 The distribution of OCT between the various organs was found to be largely the same for dogs as for human subjects *By far the largest part of the OCT was located in the liver* the amount in the human small intestine was about 14 per cent of that in the liver (per unit weight) the other organs contained only traces normal serum contained 0 001 per cent of the amount in the liver

4 Experiments on the dog gave the following results

(i) After the intravenous injection of OCT the elevated S-OCT level decreased by about 80 per cent in 24 hours.

(ii) In toxic hepatitis induced by carbon tetrachloride the S-OCT increased to 1000 times the initial value in 48 hours.

(iii) In total biliary stasis the S-OCT increased to 1000 times the initial value in 4 days and then diminished

(iv) Partial obstruction of the common bile duct increased the OCT activity in the plasma of dogs that had taken food but not of fasting dogs The OCT activity began to increase at a lower biliary pressure than did AP or bilirubin In relation to the initial values the OCT increases at higher biliary pressures were at least ten times greater than those of AP

5 Determination of the S-OCT activity in 222 apparently healthy subjects gave the following results

(i) The mean level and the variance were lower in subjects less than 26 years of age than in the older group

(ii) The frequency distribution of S-OCT was asymmetrical in both age groups The logarithms of the activity had a practically normal distribution

(iii) No diurnal variation was noted

(iv) The S-OCT activity was unaffected by vigorous physical exercise or a single large dose of alcohol

6 One half of a group of primigravidae receiving a maximum of 10 g of chloroform dripped on an open gauze mask at the second stage of labour showed a significantly higher increase in S-OCT 3 days after delivery than did a control group Similar but smal

lar differences were observed with respect to S-GOT but no significant difference in S-GPT was found. *The S-OCT level would thus appear to be a more sensitive indicator of toxic effect of chloroform on the liver than the S-GOT and S-GPT levels.*

7. Five out of 6 cholecystectomized subjects who had biliary pains following administration of morphine showed increased S-OCT levels of up to 60 times the initial value within 7 hours of the injection. Increases in S-GOT and S-GPT were recorded for only 3 of the patients, they began later than the S-OCT elevations and did not exceed 6 times the initial level. The S-AP activity increased in only one patient. *The S-OCT determination would thus seem to be more sensitive than the S-GOT, S-GPT and S-AP tests in the case of elevations in biliary pressure elicited by morphine.*

8. S-OCT determinations on 695 cases of various diseases (some 3000 serum samples) gave the following results.

(i) Increased S-OCT levels were recorded for most of the cases of liver or biliary tract diseases, such as hepatitis, cirrhosis and acute cholecystitis and in most cases of definite liver involvement, as in alcoholism, severe heart decompensation or tachycardia with fall in blood pressure. Pathologically elevated values were more common for S-OCT than for S-GOT, S-GPT or S-AP.

(ii) Elevated S-OCT was also found in some cases of heart conditions without severe decompensation, in acute enteritis, rheumatoid arthritis, systemic lupus erythematosus and allied collagen conditions. These increased levels of S-OCT, which were often accompanied by increased S-GPT, were in all probability due to leakage of OCT from the cells of the liver rather than from the cells of the small intestine.

(iii) For nearly all of the other patients with no evident liver or biliary tract disease the S-OCT activity was within normal limits.

9. Since the S-GOT, S-GPT and S-AP activities are less sensitive indexes of mild liver damage and biliary stasis of short duration than is the S-OCT activity, the determination of this enzyme activity in serum would seem to provide a useful guide in diagnosis of these conditions.

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FROM THE DEPARTMENTS OF MEDICINE (HEAD: L. WERKÖ) AND ANAESTHESIOLOGY (HEAD: K. STENBERG), SAHLGRENSKA SJUKHUSET, GÖTEBORG, SWEDEN

MYOTONIC HUMAN MUSCULATURE. STIMULATION WITH DEPOLARIZING AGENTS

Mechanical Registration of the Effects of Succinyldicholine, Succinylmonocholine and Decamethonium

By

G. ÖRNDAHL AND K. STENBERG

INTRODUCTION

There are two different ways in which muscle relaxants can affect the motor end plate. Some of these agents prevent acetylcholine from depolarizing the endplate, while others bring about a depolarization which persists and which prevents new impulses from affecting the endplate. The latter agents have an initial stimulatory effect followed by a blocking effect on the endplate. The first-mentioned agents are termed non-depolarizing, the latter depolarizing (FOLDES, 1954; THESLEFF 1955). Representative non-depolarizing agents are curare (d-TC) and gallamine. The best known depolarizing agents are succinyldicholine (SCh) and decamethonium (C_{10}). To this group also belongs succinylmonocholine (SmCh), the decomposition product of SCh, (BRÜCKE et al. 195[illegible]).

The pharmacological effects of the above-mentioned muscle relaxants have been studied in humans as well as in animals. THESLEFF (1955 b, c) utilizing intracellular micro-electrodes, studied the effect of prolonged application of SCh and C_{10} to endplates in frog muscle and rat diaphragm. The following course of events was registered: prolonged depolarization, repolarization and, finally, a period of reduced sensitivity to the transmitter substance acetylcholine.

The mode of reaction and the sensitivity to depolarizing agents varies in different animals, even in closely related species (amphibians, birds, cats and dogs; for references, see below) and may even vary from muscle to muscle in the same animal (red and white muscle in rat, JEWELL & ZAIMIS, 1954 a). Both may also vary in the same muscle under different conditions (healthy, atrophied, and denervated, for references, see below). With gradual substitution of methyl groups in C_{10} for ethyl groups, the new substances showed pro-

GÖTEBORG 1962
ELANDERS BOKTRYCKERI AKTIEBOLAG

TABLE 1

Controls with muscular or neuromuscular diseases (Control group II)

Diagnosis	Number of patient	Sex, age, (years)	Duration of disease	Clinical symptoms from registered musculature	Comments Electromyography (EMG) Pathological anatomical diagnosis (PAD)
Dystrophia musculorum progressiva	2	♂ 17 years ♀ 42 years	12 years 2 years	No paresis, no atrophy No paresis, no atrophy	Limb-girdle type EMG (biceps brachii) myopathic pattern. Limb-girdle type, PAD (deltoideus) advanced muscular dystrophy
Amyotrophic lateral sclerosis	1	♂ 48 years	3 years	Severe paresis and atrophy	PAD (right forearm) neurogenic muscular atrophy EMG (right thenar) injury to the peripheral motor neuron with denervation.
Arteria spinalis anterior syndrome (C — Th_2)	1	♂ 62 years	13 years	Severe paresis and atrophy	EMG (musc. inteross.) probably old injury of the peripheral motor neuron.
Peroneal muscular atrophy	1	♂ 42 years	> 24 years	Severe paresis and atrophy	EMG (musc. inteross.) old injury of the peripheral motor neuron.
Paresis of the finger flexors following lesion of plexus brachialis	1	♂ 32 years	12 week	Moderate paresis	PAD (hypothenar) normal muscle tissue. EMG (hypothenar and flexors of forearm) normal findings.
Same patient			20 weeks	Almost total regression of paresis	

duced B.M.R. and mental impairment as well as d. m. heredity. Among the d. m. patients investigated were three pairs of siblings. The duration of the disease in this group at the time of the investigation ranged between 6 and 33 years. Repeated determinations of serum Na, Ca, Mg, Cl and CO showed normal levels. Twenty one K values were within the normal range (3.4—5.1 mEq./L), ten were slightly above normal (max. 6.0 mEq./L). Determinations of blood cholinesterase and pseudocholinesterase were made by Augustinsson on 17 patients with myotonia, and showed values corresponding to those found in healthy subjects (Augustinsson 1956). Three of the d. m. patients were studied in connection with an operation.

gressively diminishing depolarizing characteristics in experiments on chicken gastrocnemius muscle and on the endplate of frog muscle (THESLEFF 1955 a). Since there are substances intermediate between depolarizing and non-depolarizing agents (WASER, 1958), it is natural that objections have been made to the above-mentioned classification. Thus BERGH (1953 b) among others, maintained that it was too early to draw a sharp line between the two groups of agents.

Experiments with C_{10} and d-TC on rabbit lumbrical muscle gave essentially the same results as in vitro experiments on human intercostal muscle (CHEESE et al 1957).

The effects of different muscle relaxants on healthy subjects have been studied extensively and are well documented (UNNA et al 1950; THESLEFF 1952 a; GROB et al 1956 a, among others). These relaxants moreover have been used in studies of myasthenia gravis (BENNETT & CASH 1943; BERGH 1953 a; CHURCHILL-DAVIDSON & RICHARDSON 1953; GROB et al 1956 b among others). However little is known about the effect of muscle relaxants in other muscular or neuromuscular diseases.

The purpose of this investigation was to study the reaction of myotonic musculature to stimulation with certain depolarizing agents. In a previous work it was shown that myotonic muscle is more sensitive to stimulation with acetylcholine and choline than is healthy human musculature (ÖRNDAHL, 1959). This study was designed to ascertain whether the same is true of SCh, SmCh and C_{10}. No such investigation has, to our knowledge, been published previously. A preliminary report was, however, presented by STENBERG & ÖRNDAHL (1959) and observations made by two anaesthesiologists (KAUFMAN 1960; PATERSON 1962) who used SCh and C_{10} to relax the myotonic musculature during operations, have been recorded.

MATERIAL

The investigation comprised three groups of volunteers, i. e. one group with myotonia and two control groups. One of the control groups consisted of subjects free of muscular and neuromuscular diseases, the other comprised patients with such diseases.

Patients with Myotonia

This group consisted of 14 patients, one of whom had myotonia congenita (m. c.) and the remaining 13 dystrophia myotonica (d. m.). Of these 10 were men and 3 were women, and they ranged in age from 24 to 59 years. All the myotonia patients showed both an active and a mechanical myotonic reaction as well as characteristic electromyographic findings (investigations by Petersén and Örndahl). The patient with m. c. was a heavy, powerfully built man, 77 years of age, with a familial history of this disease. All patients with d.m. had besides myotonia, paresis and atrophy of the sternocleidomastoid muscles and the extremital muscles. They had in addition one or more of the other classical symptoms of this disease, e. g. testicular atrophy, cataract, baldness, re-

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Dystrophia musculorum progressiva	2	♂ 37 years ♀ 42 years	18 years 8 years	No paresis, no atrophy No paresis, no atrophy	Limb-girdle type, EMG (biceps brachii) myopathic picture. Limb-girdle type, PAD (deltoideus) advanced muscular dystrophy
Amyotrophic lateral sclerosis	1	♂ 48 years	2 years	Severe paresis and atrophy	PAD (right forearm) neurogenic muscular atrophy EMG (right thenar) injury to the peripheral motor neuron with denervation.
Arteria spinalis anterior syndrome ($C - Th_1$)	1	♂ 63 years	15 years	Severe paresis and atrophy	EMG (musc. inteross.) probably old injury of the peripheral motor neuron.
Peroneal muscular atrophy	1	♂ 42 years	> 25 years	Severe paresis and atrophy	EMG (musc. inteross.) old injury of the peripheral motor neuron.
Paresis of the finger flexors following lesion of plexus brachialis	1	♂ 32 years	12 weeks	Moderate paresis	PAD (hypothenar) normal muscle tissue. EMG (hypothenar and flexors of forearm) normal findings.
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The effects of different muscle relaxants on healthy subjects have been studied extensively and are well documented (UNNA *et al* 1950 THESLEFF 1952 a *GROB et al* 1950 a *among others*) These relaxants, *moreover* have been used in studies of myasthenia gravis (BENNETT & CASH 1943 BEROH, 1953 a CHURCHILL-DAVIDSON & RICHARDSON 1953 *GROB et al. 1956 b* among others) However little is known about the effect of muscle relaxants in other *muscular* or neuromuscular diseases.

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Control Group I without Muscular or Neuromuscular Diseases

Control Group I comprised 21 subjects 13 men and 8 women, 16—78 years of age without prior or current muscular or neuromuscular diseases. Sixteen patients were under treatment for some disorders requiring surgery and were studied while under anaesthesia in conjunction with the operation. Five controls had internal diseases.

A 30-year-old clinically healthy brother of a d m patient was also examined

Control Group II with Muscular or Neuromuscular Diseases

Control Group II comprised 6 patients. The composition of this series is shown in Table I

METHODOLOGY

Anaesthesia. Since the agents employed give rise to apnea the examinations were made with the patients under general anaesthesia and controlled respiration when needed. Morphine scopolamine or hydromorphone atropine was given as premedication. Evipan was administered intravenously for induction and sometimes for maintenance of anaesthesia. During the experiment the patient received a mixture of N_2O and O_2 in the proportion of 2 5 to 1 in a semi-closed system The doses administered to myotonia patients and healthy controls are seen in Table II The anaesthesia was kept as constant as possible and corresponded to plane I stage III of Guedel s scheme

Administration of the Agents The agents used are listed in Table III All agents except quinine were given intravenously and as rapidly as possible in the unregistered arm After each injection the needle was thoroughly rinsed with physiological NaCl solution When injections were repeated they were separated as a rule by intervals of 5—10 minutes. The injection was usually not repeated until

TABLE II

Doses of agents used for premedication and general anaesthesia

Agent	Patients with myotonia Maximum mg	Patients with myotonia Minimum mg	Healthy controls Maximum mg.	Healthy controls Minimum mg
Morphine	12	2.5	15	10
Scopolamine	0 45	0 12	0 8	0 4
Hydromorphone	2	0.5	2.5	2
Atropine	0.5	0.125	0.42	0.3
Evipan				
Induction dose	600	150	800	200
Maintenance dose	150	50	400	50
Nitrous oxide (N_2O)	Calculations not performed			

TABLE III

Agents Used

Name of Agent	Name used by Nordiska Farmakopenämnden (Scandinavian Pharmacological Association)	Manufacturer Name of Agent
I Depolarizing Agents		
decamethonium	decamethonium	decamethonium bromid (test agent, Leo) syncurine (Burroughs Wellcome & Co)
succinyldicholine	suxamethonium	scoline, anectin (Allen & Hanbury) celocurin — jodid (Vitrum).
succinylmonocholine	—	succinylmonocholine jodid (test agent, Vitrum)
II Non Depolarizing Agents		
curare	tubocurarinum	tubocurarine chloride (Abbott).
gallamine	gallamonium	flaxedil (May & Baker).
III Other Agents		
calcium gluconat	—	calcium-Sandoz (Sandoz).
evipan	cyclobarbital (?)	evipan-natrium (Bayer).
hydromorphone atropine (0.2 % + 0.4 %)	—	hydromorfon-atropin (ACO).
morphine scopolamine (1 % + 0.4 %)	—	morfin-skopolamin (ACO).
neostigmine	neostigminum	neostigmin (Leo).
nitrous oxide (N_2O)	—	lustgas (AGA).
prostigmine	neostigminum	prostigmin (Roche).
quinine	—	chinini sulfas (ACO)

the twitches resulting from the nerve stimulation were tantamount to those preceding the injection. The SCh and SmCh solutions, which are unstable, were prepared immediately before the examination.

Data obtained from the tests of patients with myotonia are found in Table IV. Three d. m. patients were studied with SCh on repeated occasions; one patient was re-examined after an interval of five years. Two of these three patients were retested with SCh after they had received 0.75 g. quinine per day for seven days. One third of the daily dose was administered in the morning of the day of examination. In connection with the SCh tests one of these patients received 10 ml. of a 10 [illegible] calcium gluconate solution intravenously on two occasions.

The non-depolarizing agents d TC and gallamine were used in control experiments on patients with d. m.

Data from the experiments in control groups I and II will be found in Table IV and Table V respectively.

Control Group I without Muscular or Neuromuscular Diseases

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Doses of agents used for premedication and general anaesthesia

Agent	Patient with myotonia Maximum mg.	Minimum mg	Healthy controls Maximum mg.	Minimum mg
Morphine	12	2.5	13	10
Scopolamine	0.48	0.12	0.6	0.4
Hydromorphone	2	0.5	2.5	
Atropine	0.5	0.125	0.42	0.3
Evipan:				
Induction dose	600	150	600	300
Maintenance dose	150	50	400	50
Nitrous oxide (N_2O)	Calculations not performed			

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succinylmonocholine	—	succinylmonocholine jodid (test agent, Vitrum).
II Non-Depolarizing Agents		
curare	tubocurarinum	tubocurarine chloride (Abbott).
gallamine	gallaminum	flaxedil (May & Baker).
III Other Agents		
calcium gluconate	—	calcium Sandoz (Sandoz)
evipan	enhexymalum	evipan-natrium (Bayer).
hydromorphone atropine (0.2 % + 0.03 %)	—	hydromorfon-atropin (ACO).
morphine scopolamine (1 % + 0.04 %)	—	morfin skopolamin (ACO).
neostigmine	neostigminum	neostigmin (Leo)
nitrous oxide (N_2O)	—	lustgas (AGA).
prostigmine	neostigminum	prostigmin (Roche).
quinine	—	chinini sulfas (ACO).

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The non-depolarizing agents d-TC and gallamine were used in control experiments on patients with d. m.

Data from the experiments in control groups I and II will be found in Table IV and Table V respectively.

Nerve Stimulation The ulnar nerve was stimulated at elbow level throughout the experiment. A small electrode was fixed over the nerve and a larger one was placed on the upper arm The electrodes were connected to a Grass stimulator which gave rectangular current impulses with a duration of 2 milliseconds The average rate of stimulation during the experiments was 10—18 per minute with depolarizing agents and as a rule 2 per minute with d TC and gallamine. The voltage was adjusted so as to elicit the maximum muscle response (supramaxi mal" stimulation) In addition, the peroneal nerve was stimulated in one d. m patient

TABLE IV

Tests with muscle relaxants. P t ents with myotonia and healthy controls

Agent	Number of subjects	Number of series	Dose aria t ons (mg)	N mber of injections	Injections w th a positi e result)
I Isotonic registration					
Patients with dystroph a myoto ca					
succinyl dicholine	10	1	5—30	162	149 (9)
succinyl monocholine		3	10 390	17	10 (30 %)
decame-thonium	3	3	1—4	16	9 (56 %)
curare	3	5	3 15	8	0 (0)
gallamine	1	2	20—60	4	0 (0 %)
Patient w th myotonia congenita					
succinyl dicholine	1	1	10—40	7	7 (100 %)
Healthy controls					
succinyl dicholine	21	4	10—100	171	0 (0)
succinyl monocholine	1	2	200—400	5	0 (0 %)
II Isometric registration					
Pat nts with dystroph a myoto ca					
succinyldicholine	2		10—30*)	7	7 (100 %)

) The result was regarded as positi when the registered mechanical response was of sufficient magnitude for a planimetric determination of the registration figure area (> 10 mm)

) 5 injections (10 mg., 1 i jection of 40 mg., 1 injection of 30 mg.

It is sometimes difficult to elicit a maximum muscle response on stimulation of the nerv — as has been pointed out by numerous authors (LANDAU 1952; MAPLESON & MUSHIN 1955). The muscle response was not considered to have been maximal if the successive twitches showed marked inconsistencies.

Registration. The forearm and the hand were fixed in supination, the fingers semiflexed. The movements, and the tonus changes in the flexors, of the fourth and/or the fifth finger were registered by a kymograph. (Methodology: isotonic registration, THESLEFF 195_ a, isometric registration, MALMSTRÖM, 1957.) The former method was used on 41 patients and controls, the latter on two patients with d. m., one of whom was also studied via isotonic registration.

A test series of three SCh injections was given to one d. m. patient with isotonic registration from the fourth and fifth toes and stimulation of the peroneal nerve at knee level.

Because of the great individual variation in muscle strength, the amplitude of

TABLE V

Tests with succinylcholine and isotonic registration. Patients with muscular or neuromuscular disease (Control group II)

Diagnosis	Number of patients	Number of series	Dose ranations (mg.)	Number of injections	Number of injections with positive result *)
Dystrophia musculorum progressiva		3	10—20	18	8
Amyotrophic lateral sclerosis	1	2	10	8	3
Arteria spinalis anterior syndrome	1	1	10	1	0
Peroneal muscular atrophy	1	1	10	3	0
Paresis of the finger flexors, patient examined 13 weeks after lesion of plexus brachialis	1		10—20	11	6
Same patient examined 28 weeks after the injury		1	10—20	3	3
Total	6	10		34	16

*) The result was regarded as positive when mechanical response was registered.

Nerve Stimulation The ulnar nerve was stimulated at elbow level throughout the experiment. A small electrode was fixed over the nerve and a larger one was placed on the upper arm The electrodes were connected to a Grass stimulator which gave rectangular current impulses with a duration of 2 milliseconds The average rate of stimulation during the experiments was 10—18 per minute with depolarizing agents and as a rule 2 per minute with d TC and gallamine The voltage was adjusted so as to elicit the maximum muscle response (supramaximal stimulation) In addition the peroneal nerve was stimulated in one d. m patient.

TABLE IV

Tests with muscle relaxants Patient with myotonia and healthy controls

Agent	Number of subjects	Number of series	Dose variations (mg)	Number of injections	Injections with a positive result)
I Isotonic registration					
Patients with dystrophia myotonica					
succinyl dicholine	10	1	7—30	162	149 (92 %)
succinyl monocholine		3	10—300	17	10 (59 %)
decamethonium	3	3	1—4	16	9 (56 %)
curare	3	3	3—13	8	0 (0 %)
gallamine	1	2	20—60	4	0 (0 %)
Patient with myotonia congenita					
succinyl dicholine	1	1	10—20	7	7 (100 %)
Healthy controls					
succinyl dicholine	21	4	10—100	171	0 (0 %)
succinyl monocholine	1	2	200—400	9	0 (0 %)
II Isometric registration					
Patients with dystrophia myotonica					
succinyldicholine	3	2	10—250)	7	7 (100 %)

) The result was regarded as positive when the registered mechanical response was of sufficient magnitude for a planimetric determination of the registration figure area (> 10 mm²)

) 5 injections f 10 mg 1 injection of 40 mg 1 injection of 250 mg

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A test series of three SCh injections was given in one d. m patient with isotonic registration from the fourth and fifth toes and stimulation of the peroneal nerve at knee level.

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Diagnosis	Number of patients	Number of series	Dose ations (mg.)	Number of injections	Number of injections with positive result*)
Dystrophia musculorum progressiva	2	3	10–20	26	0
Amyotrophic lateral sclerosis	1	2	10	8	3
Arteria spinalis anterior syndrome	1	1	10	1	0
Peroneal muscular atrophy	1	1	10	3	0
Paresis of the finger flexors, patient examined 13 weeks after lesion of plexus brachialis	1		10–20	11	8
Same patient examined 20 weeks after the injury		1	10–20	5	5
Total	6	10		54	16

*) The result was regarded as positive when mechanical response was registered.

Nerve Stimulation. The ulnar nerve was stimulated at elbow level throughout the experiment. A small electrode was fixed over the nerve and a larger one was placed on the upper arm. The electrodes were connected to a Grass stimulator which gave rectangular current impulses with a duration of 2 milliseconds. The average rate of stimulation during the experiments was 10–18 per minute with depolarizing agents and as a rule 2 per minute with d-TC and gallamine. The voltage was adjusted so as to elicit the maximum muscle response ("supramaximal" stimulation). In addition the peroneal nerve was stimulated in one d. m. patient.

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decamethonium	3	3	1–4	16	9 (56 %)
curare	2	3	3–15	8	0 (0 %)
gallamine	1		20–60	4	0 (0 %)
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succinyl dicholine	21	4	10–100	171	0 (0 %)
succinyl monocholine	1	2	200–400	9	0 (0 %)
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Patient with dystrophia myotonica					
succinyldicholine			10–250**)		7 (100 %)

*) The result was regarded as positive when the registered mechanical response was of sufficient magnitude for a planimetric determination of the registration figure area (> 10 mm²).

**) 3 injections of 10 mg., 1 injection of 40 mg., 1 injection of 250 mg.

Patients with Myotonia

Depolarizing Agents

The results are shown in Table IV

Succinylcholine

Injection of SCh gave rise to a mechanical response of the finger flexors, causing a marked shift of the curve base line. The movement was clearly visible in both hands. Administration of 10 mg. SCh was followed, in some cases, by a tendency to wrist flexion and a slight "Geburtshelferstellung" (accoucheur's position) of the hand. With larger doses these effects became more pronounced. Large doses, moreover, resulted in an increase of the figure area formed during the mechanical response. When the dose was increased from 3 to 10 mg. the ratio of the area was 100 to ..30. When the dose was *increased from* 10 to 20 and from 10 to 40 mg. the ratio of the areas was 100 to ..00 and 100 to 150 respectively. Fig. shows the duration of three mechanical responses. The response after 40 mg. was the longest while that after ..50 mg. was almost as long as that after 10 mg.

Two patients received another series of injections after medication with quinine. A definite mechanical response was obtained with the previously effective dose of SCh. One of the patients received 10 ml. calcium gluconate (1 g.) intravenously between injections on two occasions, and still showed a definite mechanical response (Fig. 3). On five different occasions, two patients received two equal SCh injections (10 mg.) separated by so short an interval (about 1 minute) that the effect of the second injection was manifest before the mechanical response to the first injection had disappeared (double injection). The mechanical response resulting from the second injection in conjunction with the first is shown in Fig. 4. In each instance the contraction area became almost double that associated with a single equal dose.

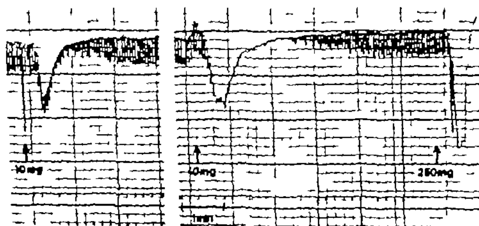


Fig. 3. Dystrophia myotonica: Examples of isometric registration of the indirect muscular twitches following supramaximal electric nerve stimulation, the response following injection of succinylcholine demonstrated by ... deep deflection of the baseline (mechanical response) and neuromuscular block of the indirect ... twitches. The apparatus ... down and registration.

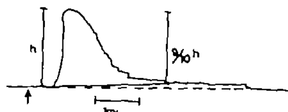


Fig 1 Dystrophia myotonica: Isotonic registration of the mechanical response following administration of *0 mg. succinyldicholine. Construction (see text) for planimetric determination of the area of the registration figure (10 4 cm² on the original figure) and for determination of margin of error (15 %) The apparatus gives upward registration.

the twitch and the mechanical response differed considerably from subject to subject and had to be modulated in some cases It was necessary to limit comparisons to the same subject in the same test series. Dosage was not based on body weight The area of the figure formed by the mechanical response and a line (broken line in Fig 1) drawn from the onset to the disappearance of the agent's stimulatory effect was planimetrically determined The duration and the intensity of the mechanical response were thus combined in a single expression. In some cases it was difficult to ascertain when the mechanical response had ceased completely In Fig 1 the area was determined when the regression according to the height line (h) marked on the diagram was nine-tenths completed. The area associated with complete regression was also determined from the diagram The difference between the two values obtained was found to be only about 15 % One of these methods of determination was used throughout each test series. Tachyphylaxis[1]) was considered to be present in a test series only when there was a decrease of more than 20 % between the first and the last figure area The planimetric values used represent the means of three determinations. The figure area after the first injection was equated to 100 and subsequent areas were determined in relation to it The resulting values were plotted in systems of coordinates (see Fig 5)

RESULTS

After administration of the anaesthetics evipan and N_2O following premedication, no registrable muscular response occurred in either the myotonia patients or the controls.

After injection of depolarizing muscle relaxants in patients with myotonia with or without concomitant nerve stimulation, there was a relatively slow flexion of the finger or a change of tonus of the finger flexors, followed by an increasingly protracted return to the initial position (mechanical response Fig 1). No mechanical response was observed after administration of d TC or gallamine The following was true of all muscle relaxants. the injections were followed by diminution or cessation of the twitches attending electrical stimulation of the ulnar nerve i e a partial or total block had arisen (Figs. 2, 3 and 4)

[1]) The decreasing responses which follow equal consecutive injections made at short intervals.

Patients with Myotonia

Depolarizing Agents

The results are shown in Table IV

Succinyldicholine

Injection of SCh gave rise to a mechanical response of the finger flexors, causing a marked shift of the curve base line. The movement was clearly visible in both hands. Administration of 10 mg SCh was followed, in some cases, by a tendency to wrist flexion and a slight "Geburtshelferstellung" (accoucheur's position) of the hand. With larger doses these effects became more pronounced. Large doses moreover resulted in an increase of the figure area formed during the mechanical response. When the dose was increased from 5 to 10 mg., the ratio of the area was 100 to 250. When the dose was increased from 10 to 20 and from 10 to 40 mg the ratio of the areas was 100 to 200 and 100 to 150 respectively. Fig 2 shows the duration of three mechanical responses. The response after 40 mg. was the longest while that after 250 mg. was almost as long as that after 10 mg.

Two patients received another series of injections after medication with quinine. A definite mechanical response was obtained with the previously effective dose of SCh. One of the patients received 10 ml calcium gluconate (1 g.) intravenously between injections on two occasions, and still showed a definite mechanical response (Fig. 3). On five different occasions, two patients received two equal SCh injections (10 mg.) separated by so short an interval (about 1 minute) that the effect of the second injection was manifest before the mechanical response to the first injection had disappeared (double injection). The mechanical response resulting from the second injection in conjunction with the first is shown in Fig. 4. In each instance the contraction area became almost double that associated with a single equal dose.

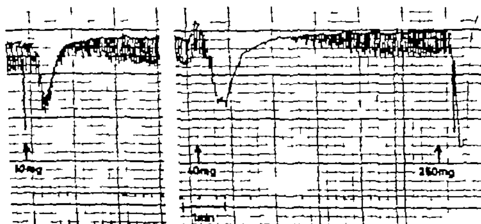


Fig. 2. Dystrophia myotonica: Examples of isometric registration of the indirect muscular twitches following supramaximal electric nerve stimulation, the response following injection of succinyldicholine demonstrated by a deep deflection of the baseline (mechanical response) and neuromuscular block of the indirect twitches. The apparatus gives downward registration.

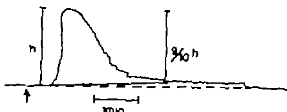


Fig 1 Dystrophia myotonica: Isotonic registration of the mechanical response following administration of 20 mg succinyldicholine. Construction (see text) f r planimetric determination of the area of the registration figure (10.4 cm on the original figure) and f deter mination of margin of error (15 %) The appa ratus gi es pward registration.

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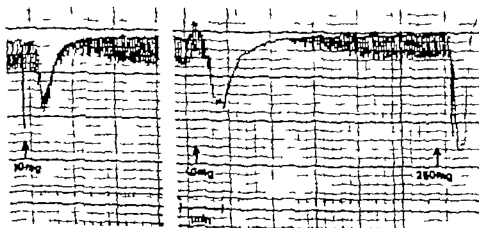


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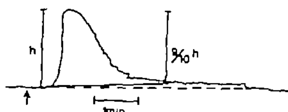


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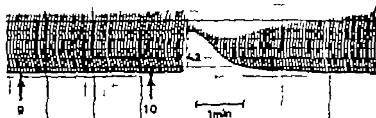
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RESULTS

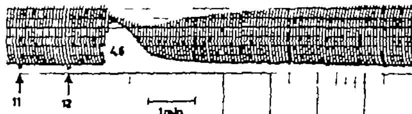
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Injection no. 9 of 0.4 mg. prostigmine no. 10 of 10 mg. SCh.



Injection no. 11 of 0.4 mg. prostigmine, no. 12 of 10 mg. SCh.

Fig. 3. Dystrophia myotonica. Isotonic registration of test series (corresponding to one of the H.G. series (the shortest) in Fig. 2) following medication with 0.75 g. quinine per day for 7 days. The first injections of 10 mg. succinyldicholine are excluded because of insufficient registration. The tracings show: Effect of succinyldicholine, calcium gluconate and prostigmine. Decrease of mechanical responses (tachyphylaxis). Increase of mechanical responses after preceding injection of prostigmine.

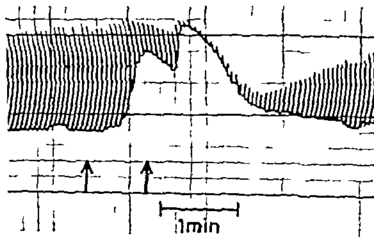
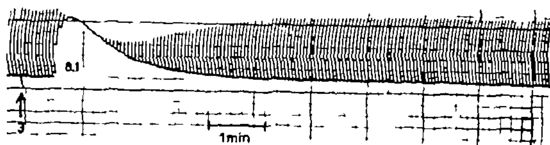
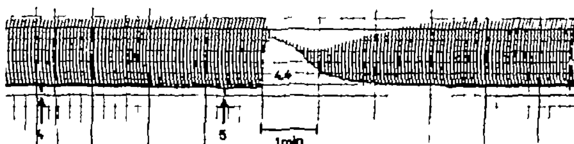


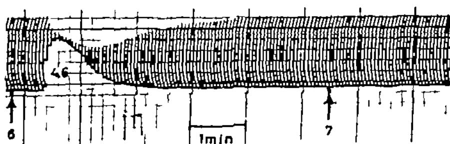
Fig. 4. Dystrophia myotonica. Isotonic registration of the mechanical response and the block after double injection of 10 mg. succinyldicholine.



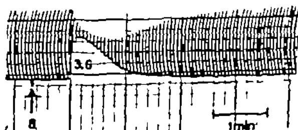
Injection no 3 of 10 mg succinyldicholine (SCh). Planimetric value of the mechanical response on the original figure = 8.1 cm²



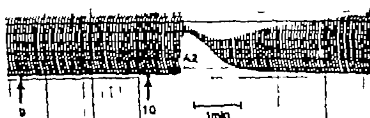
Injection no 4 of 10 ml. calcium gluconate no 5 of 10 mg. SCh.



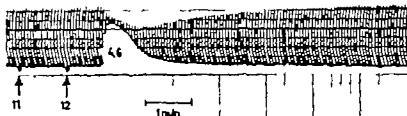
Injection no. 6 of 10 mg SCh, no. 7 of 10 ml calcium gluconat (1 g).



Injection no. 8 of 10 mg SCh



Injection no. 9 of 0.5 mg. prostigmine no. 10 of 10 mg. SCh.



Injection no. 11 of 0.6 mg. prostigmine, no. 12 of 10 mg. SCh.

Fig. 3. Dystrophia myotonica: Isotonic registration of test series (corresponding to one of the H.O. series (the shortest) in Fig. 5) following medication with 0.75 g. quinine per day for 7 days. The first injections of 10 mg. succinylcholine are excluded because of insufficient registration. The tracings show: Effect of succinylcholine, calcium gluconate and prostigmine. Decrease of mechanical responses (tachyphylaxis). Increase of mechanical responses after preceding injection of prostigmine.

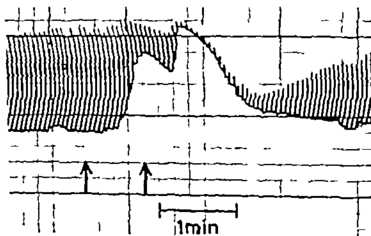
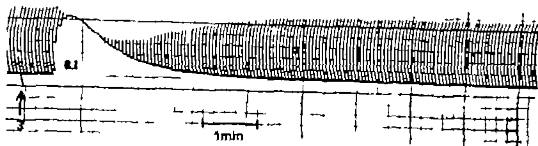
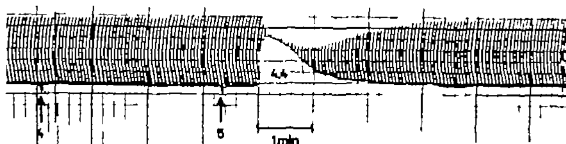


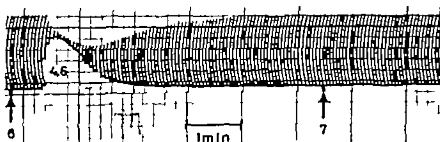
Fig. 4. Dystrophia myotonica: Isotonic registration of the mechanical response and the block after double injection of 10 mg. succinylcholine.



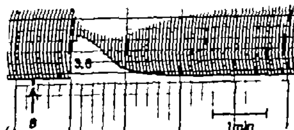
Injection no 3 of 10 mg succinyldicholine (SCh) Planimetric value of the mechanical response on the original figure = 6.1 cm²



Injection no. 4 of 10 ml. calcium gluconate no. 5 of 10 mg SCh.



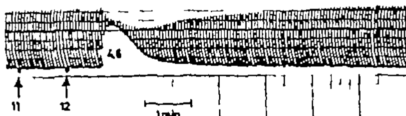
Injection no 6 of 10 mg SCh, no. 7 of 10 ml. calcium gluconate (1 g).



Injection no. 8 of 10 mg. SCh.



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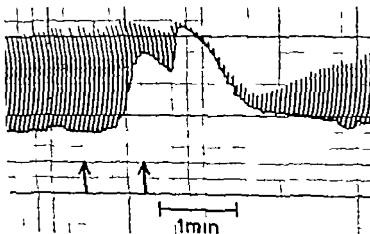
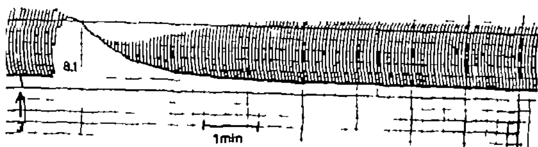
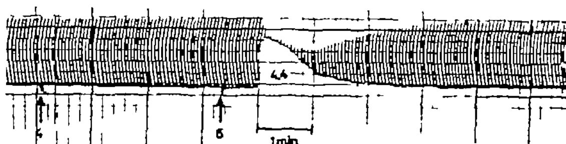


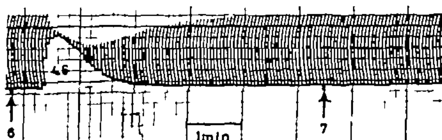
Fig 4 Dystrophia myotonica: Isotonic registration of the mechanical response and the block after double injection of 10 mg. succinylcholine.



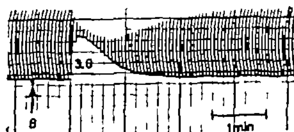
Injection no. 3 of 10 mg succinyldicholine (SCh) Planimetric value of the mechanical response on the original figure = 8.1 cm²



Injection no. 4 of 10 ml calcium gluconate, no 5 of 10 mg SCh.



Injection no 6 of 10 mg. SCh, no. 7 of 10 ml calcium gluconat (1 g)



Injection no. 8 of 10 mg SCh.

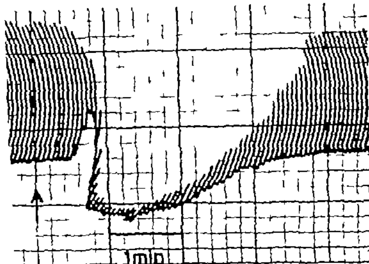


Fig. 6. Dystrophia myotonica: Isotonic registration of the mechanical response and the block following administration of 20 mg. succinylcholine, showing the effect on the extensor and flexor muscles of the fourth and fifth toes.

patient was studied with a test series of three injections the effects of which were isotonically registered from the fourth and fifth toes concurrently with stimulation of the peroneal nerve. A mechanical reaction of the extensor muscles of the toes was registered first and then a response of the flexors accompanied by a reduction in the amplitude of the twitches (Fig. 6).

On several occasions when the doses exceeded [illegible]0 mg. the mechanical response of the finger flexors was accompanied by increased resistance to insufflation of air into the lungs, pointing to a contraction-like state of the diaphragm.

The need for artificial respiration decreased with repeated equal injections of SCh (tachyphylaxis). In a test series with 10 mg. each time spontaneous breathing was interrupted for five minutes after the first injection, but only for 15 seconds after the sixth. The patient had received a total of 60 mg. during 32 minutes. Similar observations were made in six additional test series.

Succinylmonocholine

A clear mechanical response was observed in all cases after doses of 200 mg. SmCh or more. Tachyphylaxis was also noted.

Decamethonium

Only on one occasion was a *slight* response observed to follow a dose of 1 mg. C_{10}. All patients, however showed a mechanical response following injection of [illegible] mg. or more. With repeated doses of [illegible] mg. this mechanical response decreased and in one test series, disappeared altogether (tachyphylaxis).

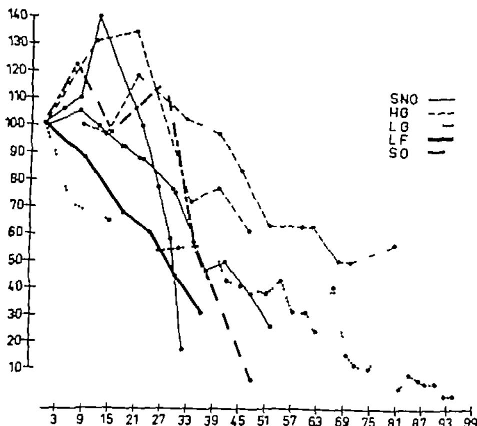


Fig. 5 Dystrophia myotonica. Test series with 10 mg. succinyldicholine showing tachyphylaxis. *Ordinate* The planimetrically determined value of the mechanical response. *Abscissa* Time in minutes. The letters represent the patient initials. In series L.G., there is a severe block (> 50 % reduction) of the indirect twit hes; in series S.N O and S O moderate block (10—50 % reduction) and in the others no block (0—10 % reduction) The first njection in one of the H.G series is ex cluded because of a technical error Do ble injections with an interval of 1—3 min tes are marked with and half the value of the mechanical responses is recorded on the figure.

Each mechanical response was followed by a more or less pronounced neuromuscular block (Figs. 2 3 and 4) the magni tude of which depended on the dose During total block after injection of 250 mg SCh it was possible to elicit a myotonic reaction by percussion

In all myotonia patients — those with d m as well as those with m c — a mechanical response and a blocking of the twitches were recorded isotonically or isometrically after injection of SCh in each series.

A comparison of the results following repeated equal injections showed that, as a rule the mechanical response decreased, i e a tachyphylactic reaction occurred (Figs. 3 and 5) This reaction developed at varying rates in different patients and even in the same patient on different occasions (*cf* series *S.N O* in *Fig 5*) In the longer series there was a diminution not only of the mechanical response but of the immediate blocking effect as well (*Fig.3*)

A mechanical response was elicited also from muscles other than the ulnar One

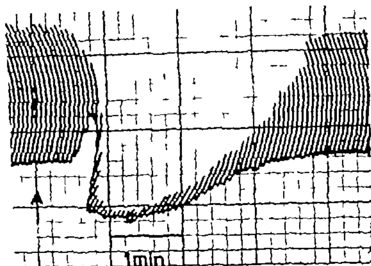


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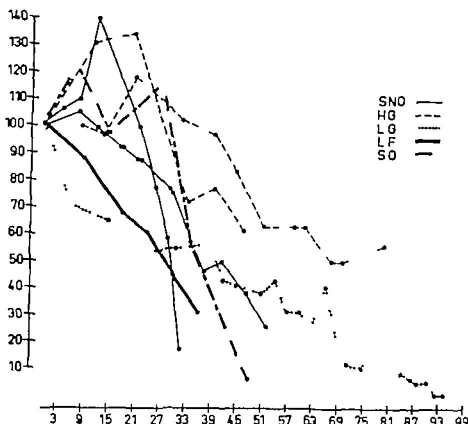


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Each mechanical response was followed by a more or less pronounced neuromuscular block (Figs. 2 3 and 4) the magnitude of which depended on the dose. During total block after injection of 250 mg SCh it was possible to elicit a myotonic reaction by percussion.

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A comparison of the results following repeated equal injections showed that as a rule the mechanical response decreased i e a tachyphylactic reaction occurred (Figs. 3 and 5) This reaction developed at varying rates in different patients and even in the same patient on different occasions (*cf* series S.N O in Fig 5). In the longer series there was a diminution not only of the mechanical response but of the immediate blocking effect as well (Fig.3)

A mechanical response was elicited also from muscles other than the ulnar One

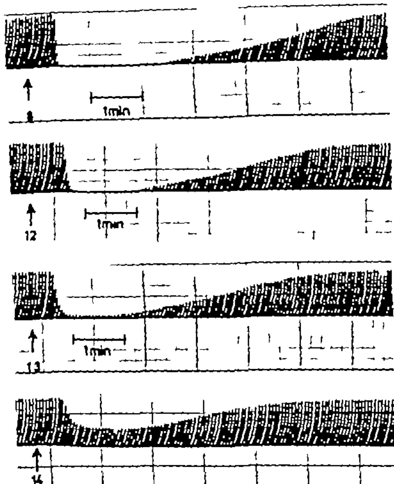


Fig. 8. Healthy control. Isotonic registration of the neuromuscular block in a series of 14 injections of succinylcholine (210 mg.) during 114 minutes shows progressively decreasing effect. The figure shows the results of injections nos. 6, 12, 13 and 14 of 15 mg. each (tachyphylaxis).

Control Group I without Muscular or Neuromuscular Diseases

The results are shown in Table IV.

Succinylcholine

No mechanical response was registered with SCh. However fasciculations were observed in some cases — usually only after the first injection of a series. Injection of 20 mg. in one subject was followed twice in one series by an increase of sub-maximal twitches prior to the block. The neuromuscular block varied in extent and duration. In several cases the block diminished progressively with repeated equal doses (tachyphylaxis). This applied to both ulnar flexor musculature (Fig. 8) and to respiratory muscles. In

Non-depolarizing Agents

The results are shown in Table IV

Curare

No mechanical response was registered after d TC but neuromuscular block was present (Fig 7) When doses of between 3 and 9 mg were given without prior injection of SCh total block did not occur No significant change of sensitivity to d TC such as that observed in e g myasthenia gravis (BENNETT & CASH 1943) was registered during those tests

Gallamine

No mechanical response, but only neuromuscular block, was registered after gallamine

Combination Tests

Injection of Succinyldicholine following Injection of Curare

Two patients with d m were tested with these two agents in three test series SCh given during regression of the block was not — unlike equal doses given prior to the d TC injections — always followed by a mechanical response of the flexors.

Anticholinesterase Administered prior to Injection of Succinyldicholine

Two patients received a series of SCh injections which resulted in tachyphylaxis. Towards the end of the test series, one of the patients was given 20 mg SCh followed 8 minutes later by 0 25 mg neostigmine, and two minutes after that by an additional 21 mg SCh The mechanical response planimetrically determined was 16 prior to injection of neostigmine and 37 afterwards. The other patient received a series of 10 mg SCh injections and towards the end of the series two doses of 0 5 mg prostigmine between successive injections of SCh The intervals between the SCh injections were 8 and 9 minutes respectively and the injections of prostigmine were given 2 ½ and 1 minute prior to the SCh injection. The ratio of the areas was 60 to 70 to 77 (Fig 3)

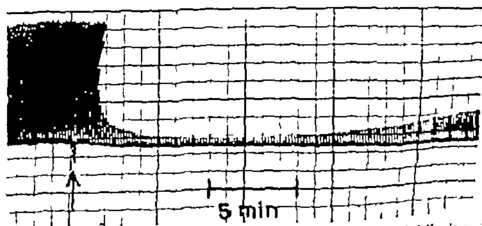


Fig 7 Dystrophia myotonica: Isotonic registration of the neuromuscular block following administration of 9 mg curare No mechanical response (straight horizontal base line)

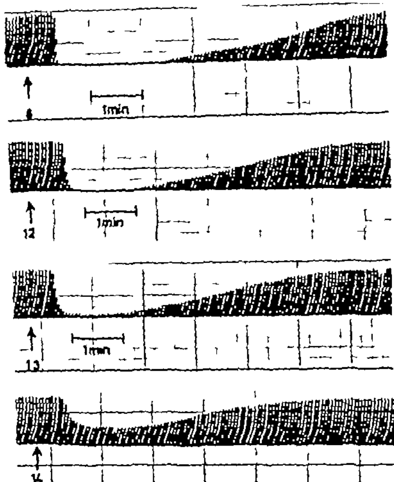


Fig. 8. Healthy control: Isotonic registration of the neuromuscular block in a series of 14 injections of succinylcholine (210 mg.) during 115 minutes shows progressively decreasing effect. The figure shows the results of injections nos. 6, 12, 13 and 14 of 15 mg. each (tachyphylaxis).

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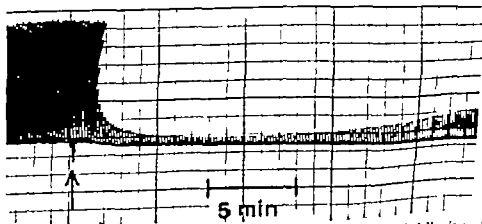


Fig 7 Dystrophia myotonica: Isotonic registration of the neuromuscular block following administration of 9 mg curare. No mechanical response (straight horizontal base line).

diminution (tachyphylaxis). In one instance an additional injection of 400 mg SmCh was given and a mechanical response of typical appearance was recorded. In one of the test series control tests were made on the left, healthy arm of the patient, and no mechanical response was observed (Fig. 9).

DISCUSSION

Depolarizing Agents

We have found, as have numerous other authors (references, see below), that healthy human musculature reacts to SCh – but not to SmCh – with fasciculations and/or an increase of indirectly elicited twitches. We have observed, moreover, that myotonic muscle – contrary to normal musculature – reacts to SCh, SmCh and C_{10} with a mechanical response. It is known that certain animal muscles react in a way which differs from that of healthy human muscle. In order to establish whether any similarity exists between myotonic human musculature and animal musculature we have compiled, from the literature, data on the reaction of certain animal muscles to depolarizing agents (Table VI).

Table VI shows that certain frog and bird muscle responds with contracture on administration of SCh, SmCh and C_{10}. The same result is observed in musculature from newborn and young mammals after SCh and C_{10} and in denervated cat muscle after C_{10}. In healthy extremital muscle of adult mammals, on the other hand, close arterial injection is followed by contraction and intravenous injection by fasciculations and an intensification of the indirectly elicited twitches. Thus myotonic muscle reacts to depolarizing agents with a mechanical response similar to that which occurs in frog and bird and denervated cat muscle, as well as in muscle from newborn and young mammals. Musculature from the human foetus also reacts to SCh with a contracture (Bergh, personal communication) and is thus, in this respect, similar to myotonic musculature. Whether the mechanical response observed in patients with myotonia is a contraction or a contracture or a combination of the two is a question which has been subjected to study. The findings will be published in a subsequent paper (Petersén, Steenberg & Örndahl, 1962).

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no case was there increased resistance to insufflation of air into the lungs.

The healthy brother of a patient with d. m. exhibited no mechanical response following three SCh injections (10 mg.)

Succinylmonocholine

Neuromuscular block but no mechanical response, was registered after SmCh.

Control Group II with Muscular or Neuromuscular Diseases

The results are given in Table V.

Patients with progressive muscular dystrophy showed no mechanical response when tested with SCh. The patient with peroneal muscular atrophy and the patient with arteria spinalis anterior syndrome likewise exhibited no mechanical response after administration of SCh. The patient with amyotrophic lateral sclerosis, however, showed a slight mechanical response after three of eight injections of 10 mg. SCh.

The patient with a right-sided paresis of the finger flexors following a plexus injury was tested on three occasions with SCh. At the last examination the only remaining sign of the injury was a slight diminution of strength. Electromyographic findings were normal, as were the histological findings in a biopsy from the hypothenar musculature. The patient received a total of 16 injections; thirteen were followed by a definite mechanical response of the type observed in cases of myotonia (Fig. 9). With repeated equal doses the mechanical response showed progressive

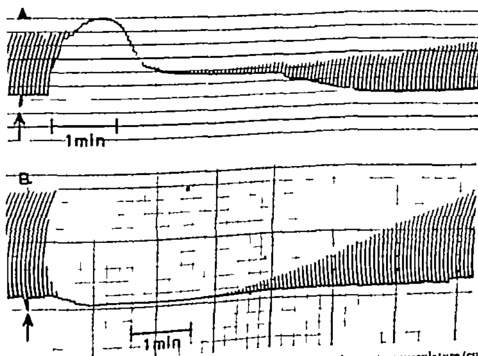


Fig. 9. Control with a plexus lesion. Isometric registration of neurogenic paretic musculature (curve A) and healthy musculature (curve B) from the same subject. Injection of 10 mg. succinyldicholine shows block on curves A and B, and mechanical response only on curve A.

diminution (tachyphylaxis). In one instance an additional injection of 400 mg. SmCh was given and mechanical response of typical appearance was recorded. In one of the test series control tests were made on the left, healthy arm of the patient and no mechanical response was observed (Fig. 9).

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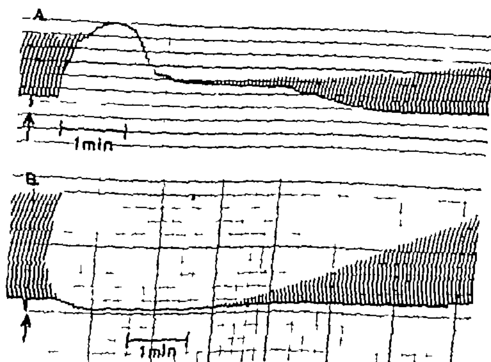


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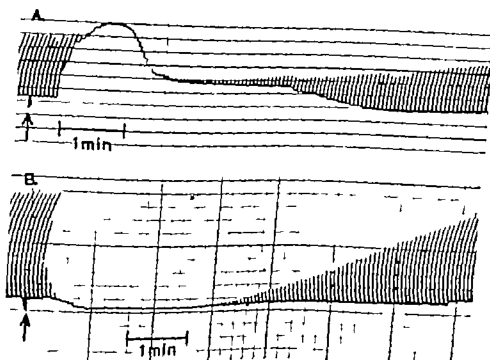


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TABLE VI

Published data on stimulating muscular effect of succinyldicholine (SCh), succinylmonocholine (SmCh) and decamethonium (C_{10}) in animals

Author and year	Muscle (Animal)	Agent	Administration	Effect
I Amphibians				
PATON & ZAIMIS (1949)	rectus abdominis (frog)	C_{10}	muscle bath	contracture
CASTELLO & de BEER (1950)	gastrocnemius (frog)	SCh	intravenous injection	contraction
GINZEL *et al.* (1951 b)	rectus abdominis (frog)	SCh	muscle bath	contracture
BRÜCKE *et al.* (195)	rectus abdominis (frog)	SmCh	intravenous injection	contracting effect
BJÖRK & WÅHLIN (1959)	gastrocnemius (frog)	SCh	intravenous injection	fasciculations
II Birds				
BUTTLE & ZAIMIS (1949)	back and neck musculature extensors of legs (pigeon, hen, chicken)	SCh + C_{10}	intravenous injection	probable contracture
GINZEL *et al.* (1951 b)	back musculature innervated and denervated gastrocnemius (pigeon)	SCh	intravenous injection	contracture
THESLEFF & UNNA (1954)	gastrocnemius (hen)	C_{10}	intravenous injection	contracture
BRÜCKE *et al.* (1953)	gastrocnemius (pigeon)	SmCh	intravenous injection	contracture
III Newborn and young mammals				
BERGH (1953 b)	diaphragm *a* (pup, kitten rabbit) *b* (guinea pig)	 *a* C_{10} *b* SCh + C	 muscle bath muscle bath	 contracture-like shortening
PURPURA *et al.* (1960)	back musculature (cat)	SCh	intravenous injection	contracture
IV Adult mammals				
a) Healthy musculature				
PATON & ZAIMIS (1949)	tibialis anterior (cat)	C_{10}	*a* intravenous injection *b* close arterial injection	*a* fasciculations, potentiation of indirect twitches, occasional contraction *b* contraction
GINZEL *et al.* (1951 c)	tibialis anterior (cat)	SCh	close arterial injection	contraction

	Muscle (Animal)	Agent	Administration	Effect
…y (1953 b)	not stated (cat)	SCh	intra-arterial or intravenous injection	fasciculations
…s (1953)	tibialis anterior and soleus (cat)	SCh	intravenous injection	fasciculations, increase of indirect twitches
…s (1953)	tibialis anterior (cat, rabbit, monkey dog)	C_{10}	intravenous or intra arterial injection	increase of indirect twitches, often in cat, rabbit seldom in dog and monkey
…all & Parkes (…53)	gastrocnemius (guinea pig) b tibialis anterior (guinea pig)	SCh + C_{10} SCh + C_{10}	intravenous injection intravenous injection	increase of indirect twitches b also contraction
Berson (1953 b)	diaphragm (gold hamster) b (rat)	SCh + C_{10} SCh + C_{10}	muscle bath muscle bath	contracture-like shortening b no contracture
Lehmann & Silk (1953)	not stated (rabbit)	SucCh	intravenous injection	slight twitches
Collier & Mac… ley (1953)	tibialis anterior (cat)	SucCh	intravenous injection	increase of indirect twitches
W… rsall (1955)	stapedius (rabbit) b tensor tympani (rabbit)	SCh + C_{10} SCh C_{10}	intravenous injection intravenous injection	prolonged, one contraction b no contraction
Hofer & Wahl (1960)	diaphragm (rat)	SCh	intravenous injection	fasciculations
b) Pathological musculature				
Jarcho et al (1951)	denervated gracilis anterior (rat)	C_{10}	intravenous injection	increased fibrillar activity contractures are not reported
Zaimis (1951)	denervated tibialis anterior (cat)	C_{10} small dose b large dose	close arterial injection close arterial injection	contraction b contraction and contracture
Jewell & Zaimis (1954 b)	tibialis anterior and soleus atrophied by tenotomy (cat)	C_{10}	intravenous injection	heightened sensitivity, increase of indirect twitches, contracture or contraction not reported.

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THESLEFF & UNNA (1954)	gastrocnemius (hen)	C_{10}	intra enous injection	contracture
BRÜCKE *et al.* (195?)	gastrocnemius (pigeon)	SmCl	intra enous injection	contracture
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[illegible]aris (1953)	tibialis anterior (cat, rabbit, monkey, dog)	C_{10}	intravenous or intra-arterial injection	increase of indirect twitches, often in cat, rabbit, seldom in dog and monkey
Hall & Parkes (1953)	gastrocnemius (guinea pig) b tibialis anterior (guinea pig)	SCh + C_{10} SCh C_{10}	intravenous injection intravenous injection	increase of indirect twitches b also contraction
Brech (1953 b)	diaphragm (gold hamster) b (rat)	SCh + C_{10} SCh + C_{10}	muscle bath muscle bath	contracture-like shortening b no contracture
Lehmann & Silk (1953)	not stated (rabbit)	SmCh	intravenous injection	slight "twitches"
Collier & Mac[illegible]ley (1953)	tibialis anterior (cat)	SmCh	intravenous injection	increase of indirect twitches
Wembrall (1955)	stapedius (rabbit) b tensor tympani (rabbit)	SCh – C_{10} SCh – C_{10}	intravenous injection intravenous injection	prolonged, tonic contraction b no contraction
Bjork & Wahlin (1960)	diaphragm (rat)	SCh	intravenous injection	fasciculations
b) *Pathological musculature*				
Jarcho et al (1951)	denervated gracilis anterior (rat)	C_{10}	intravenous injection	increased fibrillar activity contracture not reported
Zaimis (1951)	denervated tibialis anterior (cat)	C_{10} small dose b large dose	close arterial injection close arterial injection	contraction b contraction and contracture
Jewell & Zaimis (1954 b)	tibialis anterior and soleus atrophied by tenotomy (cat)	C_{10}	intravenous injection	heightened sensitivity increase of indirect twitches, contraction or contracture not reported.

TABLE VI

Published data on stimulating muscular effect of succinyldicholine (SCh), succinylmonocholine (SmCh) and decamethonium (C_{10}) in animals

Author and year	Muscle (Animal)	Agent	Administration	Effect
I Amphibians				
PATON & ZAIMIS (1949)	rectus abdominis (frog)	C_{10}	muscle bath	contracture
CASTILLO & de BEER (1950)	gastrocnemius (frog)	SCh	intravenous injection	contraction
GINZEL et al (1951 b)	rectus abdominis (frog)	SCh	muscle bath	contracture
BRÜCKE et al (1952)	rectus abdominis (frog)	SmCh	intravenous injection	contracting effect
BJÖRK & WÅHLIN (1959)	gastrocnemius (frog)	SCh	intravenous injection	fasciculation
II Birds				
BUTTLE & ZAIMIS (1949)	back and neck musculature, extensors of legs (pigeon, hen, chicken)	SCh + C_{10}	intravenous injection	probable contracture
GINZEL et al (1951 b)	back musculature innervated and denervated gastrocnemius (pigeon)	SCh	intravenous injection	contracture
THESLEFF & UNNA (1954)	gastrocnemius (hen)	C_{10}	intravenous injection	contracture
BRÜCKE et al (1952)	gastrocnemius (pigeon)	SmCh	intravenous injection	contracture
III Newborn and young mammals				
BERGH (1953 b)	diaphragm *a* (pup, kitten, rabbit) *b* (guinea pig)	C_{10} *b* SCh + C_{10}	muscle bath muscle bath	contracture-like shortening
PURPURA et al (1960)	back musculature (cat)	SCh	intravenous injection	contracture
IV Adult mammals				
a) Healthy musculature				
PATON & ZAIMIS (1949)	tibialis anterior (cat)	C_{10}	*a* intravenous injection	*a* fasciculations, potentiation of indirect twitches, occasional contraction
			b close arterial injection	*b* contraction
GINZEL et al (1951)	tibialis anterior (cat)	SCh	close arterial injection	contraction

injury was similar to those registered in our cases of myotonia. The recorded effect of SCh on the healthy arm, however was similar to that observed in normals.

When the dose of SCh was increased from 10 to 20 mg in our experiments, the stimulatory effect on the myotonic musculature became twice as pronounced. With a considerably greater increase, however e.g from 10 to 40 mg. the effect did not increase proportionately This accords with observations made by Thesleff in healthy musculature (personal communication) The reason could be that the musculature reacts in different ways t small and large doses of SCh. Churchill-Davidson *et al.* (1960) studied the effect of a massive dose of 1500 mg. SCh in healthy subject and found that it more closely approximated the effect of a non-depolarizing agent than that of a depolarizing agent.

When total neuromuscular block was present after a large dose of SCh ([illegible]0 mg) it was possible to elicit a mechanical myotonic reaction. Lanari (1947) Landau (195[illegible]) and Floyd *et al* (1953) were able to demonstrate mechanical myotonia during neuromuscular block after d TC.

Tachyphylaxis

Our results showed that the mechanical responses caused by depolarizing agents in patients with myotonia diminished progressively with repeated equal injections tachyphylaxis had set in. The fact that neuromuscularly healthy subjects usually showed fasciculations only after the first injection of SCh could also have indicated tachyphylaxis.

Hunter (19[illegible]0) reported tachyphylaxis in humans after injections of C_{10}, and Hodges *et al.* (1952) after injections of SCh. These findings, as respects both animals and humans, have been confirmed in a number of publications.

The cause of the tachyphylactic phenomenon has not yet been fully established. In studying SCh and C_{10}, Zaimis (1953) and Paton (1953) concluded that these agents cause, in many mammals, a depolarizing block which in some respects resembles that caused by non-depolarizing agents. A common characteristic of these blocks is that they reduce the effect of the stimulation brought on by repeated injections of depolarizing agents. This, according to Zaimis, may be the explanation of tachyphylaxis Foldes *et al.* (1957) believed that a prolonged administration of depolarizing gents to the endplate alters the receptors in such a way that they develop a resistance to the depolarizing effect of these agents.

In two test series, one on a patient with d. m., and the other on a healthy subject SmCh injections were substituted for some of the SCh injections. E en after this substitution tachyphylaxis occurred. This had not been previously demonstrated

Cholinesterase Inhibitors

Anticholinesterases such as prostigmine and eserine, when injected shortly before administration of depolarizing agents, have a potentiating effect on the latter (Foldes, 1957), which probably results from reduced decomposition of these agents (Castello & de Beer, 19[illegible]0). Stable cholinesters and other quaternary

and, on occasion an increase of the twitches elicited by stimulation of the ulnar nerve. Similar behaviour was observed in one of our controls. The curves recorded from our healthy controls corresponded closely with those obtained by THESLEFF (1952 a). UNNA *et al.* (1950) reported fasciculations in 25 % of a group of conscious healthy volunteers after injections of small doses of C_{10} which gave rise to partial block. FOLDES *et al.* (1954) observed no stimulatory action by SmCh in healthy subjects. Nor was any such effect observed in our control subject.

All our myotonia patients — unlike the healthy controls — exhibited a rather prolonged mechanical response of the flexors of the fourth and/or fifth finger following injections of SCh, SmCh and C_{10}. After doses of 20 mg or more there occurred a slight flexion of the wrist and an accoucheur's position of the hand. No report of such a reaction in humans could be found in the manuals on muscular and neuromuscular diseases (ADAMS *et al.* 1960; BOURNE 1960; ADAMS *et al.* 1962) in the manuals on anaesthesiology (VON MANN 1954; GRAY 1959) in the compilations of clinical observations of myotonia (DE JONG 1956; PIPBERGER, 1956) or in the collected results of SCh and C_{10} tests (HEWER, *et al.* 1949; ELLERKER, 1950; HARRIS & DRIPPS, 1950; FOLDES & MACHAJ 1951; BOURNE *et al.* 1952, VON DARDEL & THESLEFF 1952, HOLMBERG & THESLEFF 1952; RIZZI & RICCI 1953; CARLSON *et al.* 1954; POULSEN & HOUGS 1957). We have found in the literature only seven myotonia cases tested with depolarizing relaxants; six received SCh and one C_{10}. In four of these cases (BOURNE & ZUCK 1957; HUNTER, 1960; KAUFMAN 1960) no mechanical response was reported. In the three other cases, it was stated that SCh and C_{10} produced myotonia (KAUFMAN 1960; PATERSON 1962).

The duration of the total muscular effect of SCh in our myotonic patients was not markedly greater than that referable to healthy controls. This finding — which has not been previously communicated — applied both to respiratory muscles and to ulnar flexor muscles. Zaimis (1953) demonstrated, in different animals, an inverse relationship between the sensitivity to blocking by C_{10} and the sensitivity to blocking by d-TC. Since myotonic muscle has an elevated sensitivity to the stimulatory action of SCh and C_{10}, a diminution of the sensitivity to d-TC might be expected. This has not been affirmed by our experiments, nor by previously reported observations (DUNDEE, 1952; LODGE, 1958).

In cases of d. m. the lower leg muscles also show myotonic characteristics though not as pronounced as those of the finger flexors (THOMASEN 1948). In our study of the muscles of the two fibular toes we found that these muscles too reacted with a mechanical response. The myotonic nature of the diaphragm musculature in cases of m. c. has been previously reported (PIPBERGER 1956). After injection of SCh in patients with d. m. we observed a contraction-like condition of the diaphragm. Lindell (personal communication) has observed a mechanical response in the masseter muscles of patients with d. m. shortly after injection of SCh.

The curve recorded after intravenous SCh injections in a patient with paresis of the finger flexors following a plexu

injury was similar to those registered in our cases of myotonia. The recorded effect of SCh on the healthy arm, however was similar to that observed in normals.

When the dose of SCh was increased from 10 to 20 mg in our experiments, the stimulatory effect on the myotonic musculature became twice as pronounced. With a considerably greater increase however e.g. from 10 to 40 mg, the effect did not increase proportionately. This ccords with observations made by Thesleff in healthy musculature (personal communication). The reason could be that the musculature reacts in different ways to small and large doses of SCh. CHURCHILL DAVIDSON et al. (1960) studied the affect f massive dose of 1,000 mg. SCh in a healthy subject and found that it more closely approximated the effect of a non-depolarizing agent than that of a depolarizing agent.

When total neurom scular block was present after a large dose of SCh (250 mg.), it was possible to elicit a mechanical myotonic reaction. LANARI (1947), LAND U (1952) and FLOYD et al. (1956) were able to demonstrate mechanical myotonia during neuromuscular block after d-TC.

Tachyphylaxis

Our results sho ed that the mechanical responses caused by depolarizing agents in patients with myotonia diminished progressively with repeated equal injections i.e. tachyphylaxis had set in. The fact that neuromuscularly healthy subjects usually showed fasciculations only after the first injection of SCh could also be indicated tachyphylaxis.

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In two test series, one on a patient with d. m., and the other on a healthy subject SucCh injections were substituted for some of the SCh injections. Even after this substitution tachyphylaxis occurred. This had not been previously demonstrated.

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Anticholinesterases such as prostigmine and eserine, when injected shortly before administration of depolarizing agents, have a potentiating effect on the latter (FOLDES, 1957), which probably result from reduced decomposition of these agents (CASTILLO & DE BEER, 1950). Stable bolinesters and other quaternary

ammonium compounds are also potentiated by these inhibitors, probably because the inhibitors increase the non specific irritability of the effector cells in the endplate (ZAIMIS 1951 BLABER & BOWMAN 1950) THESLEFF (1952 b) has shown that fasciculations caused by SCh in the cat are intensified and prolonged by anticholinesterases. Our investigations showed that in myotonia patients the mechanical response caused by SCh is increased by anticholinesterases.

Non-depolarizing Agents

The non-depolarizing relaxants produce as a rule no stimulation of striated muscle (PATON & ZAIMIS, 1952) Only under special conditions has stimulation been observed (FOLDES 1950) RIKER & WESCOE (1951) noted that gallamine could cause a slight increase of the indirectly produced twitches, if administered in amounts which did not cause block. Gallamine (in muscle bath) caused stimulation of toad sartorius muscle (BERGH 1953 b) Denervation of muscle increases its sensitivity to d TC and gallamine both in amphibians and in mammals (MCINTYRE *et al* 1945 BÜLBRING & DEPIERRE 1949 JARCHO *et al* 1950) Intravenous injection of d TC and gallamine in our patients with d m was followed only by a neuromuscular block similar to that observed in normal subjects. These observations accord with those of other authors who have studied d m patients after intra-arterial or intravenous injections of d TC Thus they reported no stimulation (LANARI 1947 DUNDEE 1952 LANDAU 1952

Interference of Curare with Succinyl dicholine

Administration of a non-depolarizing relaxant reduces the blocking effect of a subsequent dose of depolarizing relaxant both in mammals (PATON & ZAIMIS 1949 GINZEL *et al* 1951 a among others) and in humans (MACFARLANE *et al* 1950 CHURCHILL-DAVIDSON 1956 FOLDES *et al* 1957) Our studies of patients with d. m showed this to be true as respects the stimulating effect of SCh administered after injection of d TC.

Other Agents

Tests with depolarizing agents were made on patients under evipan N_2O anaesthesia after premedication with a morphine drug in combination with scopolamine or atropine. Our experiments showed that the premedication and the anaesthesia did not influence the indirectly produced twitches, nor as far as we could see did they affect the mechanical myotonia. The anaesthetics administered should therefore be of little significance as respects the results of our experiments

It is generally known that quinine reduces the myotonic reaction (WOLF 1936 KENNEDY & WOLF 1937 LINDQVIST 1943) but even after receiving this agent our patients showed a mechanical response following injection of SCh One of our patients received intravenously injected calcium gluconate which according to THOMASEN (1948) and SIIRALA (1940) increases the effect of quinine However this did not abolish the mechanical response which occurred after 10 mg SCh

These experiments thus indicated that myotonic musculature is highly susceptible to the stimulatory action of SCh

Electrolytes and Cholinesterases

It is known that the neuromuscular transmission and the action of muscle relaxants are affected by disturbances of the electrolytic balance (FOLDES, 1959). The action of SCh may moreover vary with the pseudo-cholinesterase content (EVANS et al., 1952; LEHMANN & RYAN 1956, among others). In our myotonia cases the electrolyte values were normal except for some slightly elevated potassium values. Furthermore, determination of pseudo-cholinesterase in 12 myotonia patients showed normal values. Thus, the mechanical response which occurs after administration of depolarizing agents cannot be attributed to disturbances of the serum electrolyte balance or to plasma pseudo-cholinesterase level.

Control Group II with Muscular or Neuromuscular Diseases

The patient with peripheral paresis of one arm as a result of plexus lesion showed a mechanical reaction after intravenous injections of SCh — even when almost total regression of the paresis was present. There was, however no mechanical response of the musculature in the healthy arm. The peripheral nerve damage thus seems to be a prerequisite for the occurrence of a mechanical response. The paretic musculature of this patient thus responded to a depolarizing agent in the same way as myotonic musculature and denervated cat muscle. In about half the tests the patient with amyotrophic lateral sclerosis showed a slight mechanical response after SCh. This could have been attributable to the presence of denervated muscle fibres. This patient had shown symptoms of the disease for three years. In no case, however did patients with arteria spinalis anterior syndrome or peroneal muscular atrophy show a mechanical response. This may have been due to the absence of denervated muscle fibres. In these patients the injuries to the peripheral motor neuron were of more than 13 years duration. Patients with primary muscle disease likewise exhibited no mechanical response after injection of SCh

SUMMARY

The myotonic musculature of 13 patients with dystrophia myotonica and one patient with myotonia congenita was studied through stimulation with intravenously administered depolarizing muscle relaxants (succinyldicholine 162 injections, succinylmonocholine 17 injections, and decamethonium 16 injections). Control experiments were made with non depolarizing muscle relaxants (curare 8 injections and gallamine 4 injections) in patients with dystrophia myotonica. Similar experiments were also conducted with succinyldicholine (171 injections) and succinylmonocholine (9 injections) on 1 healthy subjects and with succinyldicholine (52 injections) and succinylmonocholine (1 injection) on 6 controls with

ammonium compounds are also potentiated by these inhibitors, probably because the inhibitors increase the nonspecific irritability of the effector cells in the endplate (ZAIMIS, 1951 BLABER & BOWMAN 1959) THESLEFF (1952 b) has shown that fasciculations caused by SCh in the cat, are intensified and prolonged by anticholinesterases. Our investigations showed that in myotonia patients the mechanical response caused by SCh is increased by anticholinesterases.

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muscular or neuromuscular diseases The studies were conducted with the patients under general anaesthesia The effects were recorded isotonically and on two occasions, isometrically as well.

1 In each series all myotonia patients showed a mechanical response of the ulnar flexor muscles after injection of succinyldicholine succinylmonocholine and decamethonium — a phenomenon not previously studied in humans. Patients with dystrophia myotonica manifested a similar phenomenon in the flexors and extensors of the toes and in the diaphragm Succinyldicholine in doses exceeding 20 mg resulted in flexion of the wrist and an accoucheur's position of the hand The healthy controls showed no mechanical response after the administration of succinyldicholine and succinylmonocholine

Of controls with muscular or neuromuscular diseases one patient with amyotrophic lateral sclerosis exhibited a slight mechanical response after a few injections of succinyldicholine Furthermore one patient with peripheral neurogenic paresis of the finger flexor showed a definite mechanical response of the paretic musculature similar to that observed in patients with myotonia When tests were made on the healthy arm of this subject however the reaction was equivalent to that observed in normals.

2 With repeated injections of succinyldicholine succinylmonocholine and decamethonium in patients with dystrophia myotonica the effect of the stimulation progressively decreased (tachyphylaxis) It was observed moreover that with higher doses of succinyldicholine the mechanical response did not increase in proportion to the dose

3 When total neuromuscular block was present after succinyldicholine, it was possible to elicit a myotonic reaction by percussion.

4 Myotonic muscle showed a heightened sensitivity to the stimulatory action of succinyldicholine succinylmonocholine and decamethonium and reacted in a manner similar to that described in the literature with respect to certain muscles of the frog and the bird musculature of newborn and young mammals, and denervated cat muscle It was also shown that myotonic muscle and neurogenic peripheral paretic human muscle reacted in the same way

5 Intravenous injection of the non-depolarizing relaxants curare and gallamine in patients with dystrophia myotonica had no stimulating effect The reaction was identical with that described for normals

6 The stimulatory action of succinyldicholine in patients with dystrophia myotonica was enhanced by anticholinesterase and reduced by curare

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MYOTONIC HUMAN MUSCULATURE STIMULATION WITH DEPOLARIZING AGENTS

Simultaneous Mechanical and Electromyographic Registration

By

I. PETERSÉN, K. STENBERG AND G. ÖRNDAHL

INTRODUCTION

The mechanism underlying the myotonic phenomenon following voluntary innervation in patients suffering from myotonia congenita (m.c.) or dystrophia myotonica (d.m.) is not known. In order to study this phenomenon — the active myotonic phenomenon — depolarizing agents have been used, e.g., the natural transmitter substance acetylcholine[1]) (LANARI, 1936, EKOBAEK, 1951, ÖRNDAHL, 1962) and its decomposition product choline[1]) (ÖRNDAHL, 1962) as well as the depolarizing muscle relaxants decamethonium[1]) and succinylcholine[1]) and the latter's decomposition product, succinylmonocholine (ÖRNDAHL & STENBERG 1962). All these agents have an initial stimulatory effect followed by a blocking effect on the motor endplate in animals as well as in humans. In patients with myotonia these agents give rise to a pronounced muscular effect which can be registered either isotonically or isometrically. Only ACh produces such mechanically registrable effect in normal subjects; other agents are either devoid of effect or simply cause fasciculations. In experiments on frog and bird muscle and mammalian foetus musculature, this mechanically *registrable effect* has been studied and described (for references *vide* ÖRNDAHL, 1962; ÖRNDAHL & STENBERG 1962). It has also been observed in denervated cat muscle (ZAIMIS, 1951) and paretic muscle from a patient with plexus lesion (ÖRNDAHL & STENBERG 1962). The non-depolarizing agents curare and gallamine have produced, in patients with myotonia, no registrable stimulatory effect (ÖRNDAHL & STENBERG 1962) but only flaccid paresis (block) as in normal subjects. Myotonic muscle thus reacts to

[1]) Abbreviations used: acetylcholine = ACh, choline = Ch, succinylcholine = SCh, decamethonium = C_{10}.

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depolarizing agents with a mechanical response similar to that of muscle from frog, bird and mammalian foetus, as well as that of denervated cat muscle and paretic human muscle following plexus lesion. It is known that in the abovementioned animals the muscular response to the depolarizing agents used consists of contraction as well as contracture. The former, unlike the latter, is associated with electrical activity in the form of action potentials.

This investigation was undertaken in order to establish whether the relevant phenomenon in myotonic muscle consists of contraction, contracture or a combination of the two. Simultaneous mechanical and electromyographic registration was used. Preliminary results have been discussed previously (ÖRNDAHL *et al.*, 1961).

MATERIAL

The series comprised two groups of volunteers — one group with myotonia and a control group without muscular or neuromuscular diseases. In addition, one patient with a peripheral nerve lesion was studied.

Patients with Myotonia

This group consisted of 12 patients, two of whom had m.c. (a 32-year-old man and a 50-year-old woman) and the remainder d.m. (9 men and 1 woman, 35–61 years of age). All the patients showed active and mechanical myotonic reactions. The woman with m.c. was free from subjective symptoms, but exhibited a mechanical myotonic reaction. Her father, who had typical symptoms of m.c., is included in another series (ÖRNDAHL & STENBERG, 1962). In addition to myotonia the patients with d.m. had paresis and atrophy of the sternocleidomastoid muscles and of the extremital musculature besides one or more of the classical symptoms of this disease, e.g. testicular atrophy, cataract, baldness, reduced B.M.R. and mental deterioration, as well as d.m. heredity. Biopsies were taken from the forearm muscles of four patients. The histological picture corresponded well with previously described findings in patients with d.m. All the patients were subjected to diagnostic electromyographic examinations which showed the well known pattern, dominated by signs of increased mechanical irritability and conforming closely to previously published findings (LINDSLEY & CURNEN, 1936; BUCHTHAL & CLEMMESEN, 1941; WEDDELL *et al.*, 1944; KUGELBERG & PETERSÉN, 1949; FLOYD *et al.*, 1955; VON EIFF, 1960).

Controls

The control group consisted of 4 subjects, 2 men and 2 women, 32–60 years of age, without muscular or neuromuscular diseases. These controls had been admitted for surgical diseases (varices, hernia, etc.) and were studied while under anaesthesia in connection with the operation.

A 40-year-old man with a 14-day-old injury of the left brachial plexus but otherwise healthy, was also investigated. The injury had given rise to paralysis and anaesthesia of the left arm.

METHODOLOGY

Anaesthesia

Since injections of ACh, Ch, SCh, and C_{10} in the doses here employed, cause muscular pain — and the last two agents apnea as well — the examinations were carried out under evipan-nitrous oxide anaesthesia following premedication with morphine scopolamine or hydromorphone atropine. One patient with d.m. was studied after nerve block, the patient with a plexus injury was examined without anaesthesia.

Administration of the Agents

The number of subjects tested, the agents injected, the number of injections, and the doses are shown in Table I.

ACh and Ch were given intra-arterially through a polyethylene catheter introduced in the proximal direction into the brachial artery at elbow level. The arterial circulation was not interrupted. In ten patients SCh and C_{10} were given intravenously through needles subsequently rinsed with physiological saline and in six

TABLE I

Pharmacological tests on myotonic patients and controls

Agent	Number of subject	Number of series	Number of injections intra-art.	Number of injections intraven.	Dose variations in mg. intra-art.	Dose variations in mg. intra-ven.	Mechanically repeatable effect
I Patients with dystrophia myotonica or myotonia congenita (Fig. in brackets)							
Acetyl-choline	7 (2)	7 (2)	40 (14)		0.04 – 13		all patients
Choline	4	4	7		2 – 40		all patients
Succinyl-dicholine	7 (2)	9 (2)	2 (3)	19	5 – 30	10 – 150	all patients
Decame-thonium	2	2	3	1	1	3	all patients
II Neuromuscularly healthy controls							
Acetyl-choline	3	3	21		0.04 – 20		none
Choline	2	2	15		3 – 40		none
Succinyl-dicholine	1	1		1		25	none
Decame-thonium	1	1		2		2 3	none
III Patient with paralysis following plexus lesion							
Acetyl-choline	1	1	7		0. 6 – 20		effect
Choline	1	1	6		10 – 40		no effect

2

depolarizing agents with a mechanical response similar to that of muscle from frog bird and mammalian foetus as well as that of denervated cat muscle and paretic human muscle following plexus lesion. It is known that in the above-mentioned animals the muscular response to the depolarizing agents used consists of contraction as well as contracture The former unlike the latter is associated with electrical activity in the form of action potentials

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A 40-year-old man with a 12-day-old injury of the left brachial plexus but otherwise healthy was also investigated The injury had given rise to paralysis and anaesthesia of the left arm

P tients with Myotonia

Intra-arterial injection of the *four de* polarising agents (ACh, Ch SCh and C_{10}) gave rise to an electromyographically registrable effect — usually within about .5 seconds, with variations from .. to 8 seconds. On intravenous injection of SCh and C_{10}, the latent period was, as a rule, about 30 seconds with variations from 20 to 44 seconds. These latent periods represented the pproximate time required for the injected agents to reach the muscle where the needle electrode was positioned. The circulation time from one arm to the fingers of the opposite arm is, according to WARBURG (1946), between 16 and .5 seconds.

After bout one half of the injections, an electromyographic effect was recorded almost simultaneously in the hypothenar and in the long flexor After most of the thers it was registered first in the hypothenar

On intra-arterial administration the maxim m mechanical effect was generally observed within 3—11 second after the first registrable effect. The corresponding time for intravenous ad ministration as, a rule 10—20 seconds

No essential differences were observed n the effects of the four agent on myotonic muscle SCh nd C_{10} produced similar effect whether given intra-arterially or intra enously Patients with d.m. and m showed similar reactions to ACh and SCh A mechanical as well as an electromyographic effect w recorded in all myotonia patients after depolarising gent (Table I).

Acetylcholine

The effects of equal doses of ACh varied in the individual as well as from patient to patient. Thus on several occasions a given dose was found to produce a muscular effect in one patient but not in another In one case, a dose of ACh (0.25 mg.) resulted in a registrable effect but a larger dose (0.50 mg.) gave no effect in the same patient at the same study As a rule no ffect was observed with a dose of less than 1 mg In one case (the woman with d.m) doses between 5 and 15 mg failed to produce muscular effects — probably due to the presence of arterial spasm clinically manifest in pulselessness, bsence of sweating, and redness of the skin of the forearm and hand. The duration of the effects increased, as a rule, w th increase of dose administered. In one patient the effect of 0 5 mg. lasted about 4 seconds, that of 1 mg bout 15 seconds, and that of 5 mg more than 30 seconds.

A substantial difference was observed between the results of the less effective doses and those of the highly effective ones. Injection of a dose as large as 10 mg. prod ced the following reaction in myotonic muscle. While the mechanical effect was in progress, interfering activity was registered both in the long flexor and in the hypothenar Thi activity diminished at a more rapid rat than the mechanical effect dur ing regression, and in some instances eased entirely despite a persisting mechanical effect (Fig 1). Comparison of mechanical effects of uniform amplitude at the outset of progression and t the end of regression showed that the electrical activity had been reduced considerably

patients the SCh and C_{10} injections were given intra arterially. All solutions were injected as rapidly as possible. About 10% of the administered volume remained in the catheter and did not enter the circulation until the next injection. Since rising concentrations were usually employed for serial injections, the error associated with the catheter volume was of no major significance.

Nerve Stimulation

The ulnar nerve was stimulated at the elbow. For this purpose a Grass stimulator with an isolating unit connected between the stimulating electrode and the apparatus was employed. The stimulator produced rectangular impulses with a duration of about 1 millisecond. The voltage was so adjusted as to give, when possible, a maximum muscle response. The frequency of stimuli was 1 per second, in some cases 2 per second.

Registration

The forearm and hand were fixed in supination. The three ulnar fingers were slightly flexed at the metacarpo-phalangeal joints and otherwise extended. The ungual phalanges were attached to a metal plate, the slightest movements of which activated, via a strain gauge, one of the channels of a Disa electromyograph. In this manner the change of tonus (mechanical effect) in the musculature of these fingers was recorded. The resultant tracing is indicated by the symbol *a* in the figures. The other two channels of the electromyograph were used for recording muscle action potentials, concentric needle electrodes with an outer diameter of 0.65 mm. being employed for this purpose. An earth lead was placed between the proximal needle electrode and the stimulation electrode. Tracings were recorded from one of the long flexors (*b* in the figures) of the forearm — usually the flexor carpi ulnaris which is readily identified. In some instances the needle electrode was inserted at various points, into the flexor group of the forearm, so that tracings were obtained from some of the other muscles. Recordings were also obtained from the hypothenar (*c* in the figures), i.e. from the flexor digiti quinti brevis or from the abductor digiti quinti muscle, which is instrumental in the flexion of the little finger (e.g. WELLS 1955). These muscles, both of which are innervated by the ulnar nerve, have in part a common origin and a common insertion and often form a unitary muscle (e.g. RAUBER & KOPSCH 1940).

RESULTS

Patients with myotonia showed spontaneous electrical activity and mechanical irritability whether under narcosis or not. This was confirmed by the electromyograms recorded while the patients were conscious or under narcosis prior to administration of depolarizing agents. On examination of neuromuscularly healthy controls moreover we observed that the narcosis did not affect the mechanical irritability as tested through motions of the needle electrode. The electromyographic characteristics of these needle motions have been described by KUGELBERG & PETERSEN (1949).

Intra-arterial injection of the four depolarizing agents (ACh, Ch SCh and C_{10}) gave rise to an electromyographically registrable effect — usually within bout 5 seconds, with variations from 2 to 8 seconds. On intravenous injection of SCh and C_{10}, the latent period was, as a rule, bout 30 seconds with variations from 20 to 44 seconds. These latent periods represented the approximate tim required for the injected agents to reach the muscle where the needle electrode was positioned. The circulation time from one arm to the fingers of the opposite arm is, according to WARBURG (1946), between 16 and .3 seconds.

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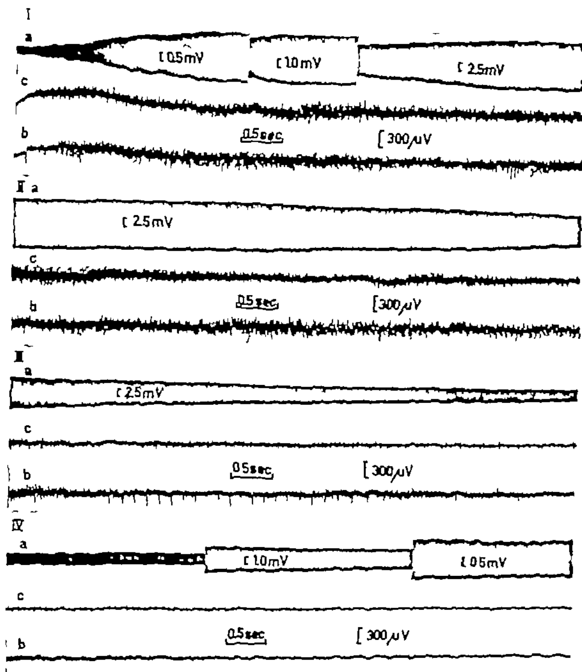


Fig. 1. Dystrophia myotonica, simultaneous mechanical and electromyographic registration after 10 mg acetylcholine intra-arterially. The curves are divided into 4 continuous sections (I—IV). a: mechanically registered tonus change in the ulnar flexor muscles (mechanical effect). b: electromyographic registration from the flexor carpi ulnaris muscle. c: from the hypothenar. The electrical activity ceases despite a remaining mechanical effect. The duration of the mechanical effect is about 4[illegible] seconds.

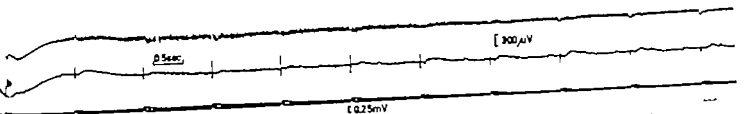


Fig. 2. Dystrophia myotonica, 0.4 mg. acetylcholine intra-arterially. Mechanical effect of about 6 seconds duration. Then remaining electrical activity in (hypothenar). Effect from ulnar stimulation.

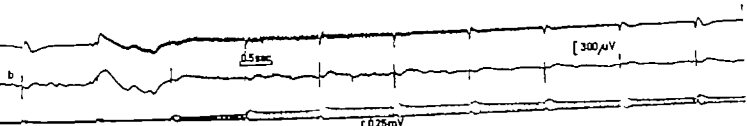


Fig. 3. Dystrophia myotonica, 2 mg   holine intra-arterially. Mechanical effect of about 8 seconds duration.

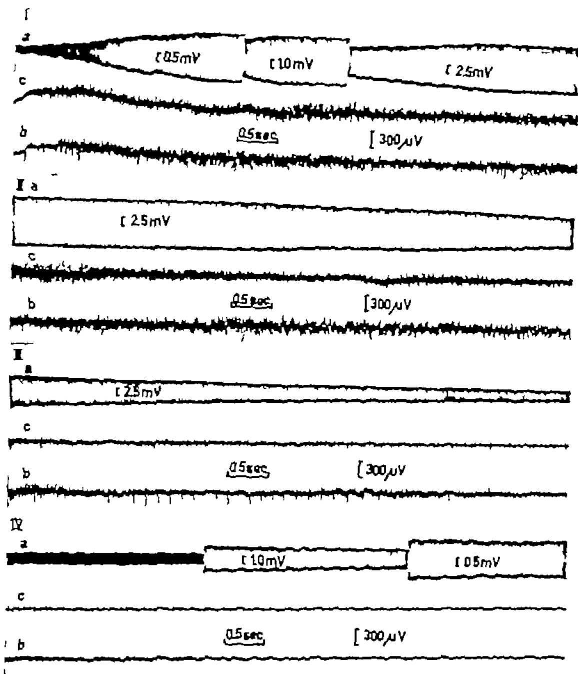


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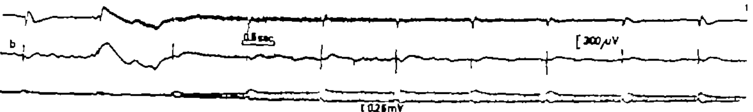


Fig. 3. Dystrophia myotonica, 2 mg. choline intra-arterially. Mechanical effect of about 8 seconds duration.

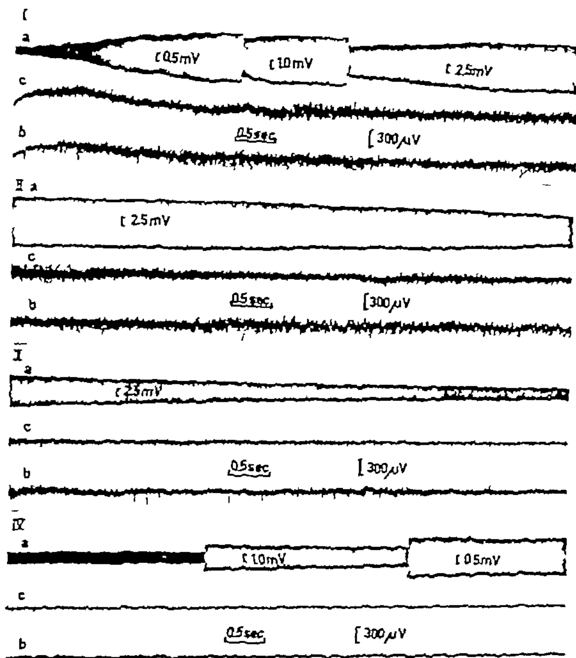


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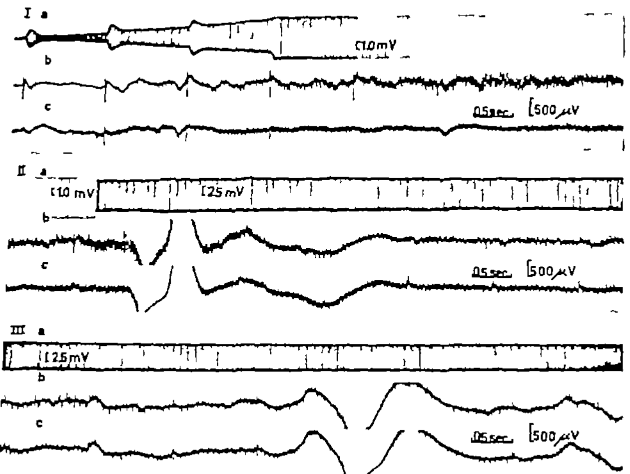
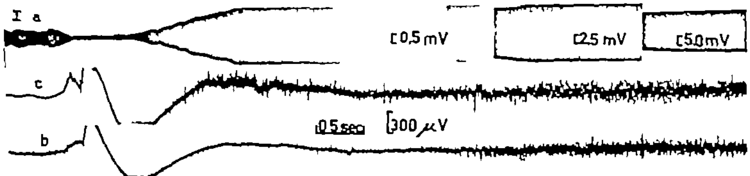
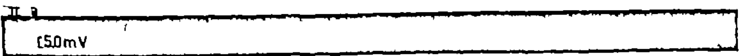
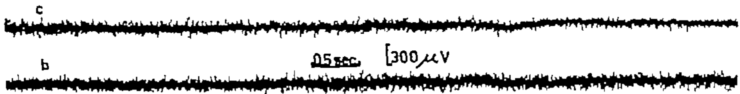
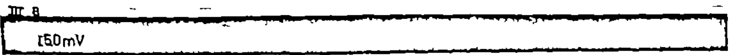


Fig. 8. Dystrophia myotonica, 80 mg. succinylcholine intra-venously. Results as in Fig. 1. The effect of the low stimulation ceases. Mechanical effect of about 80 seconds' duration.











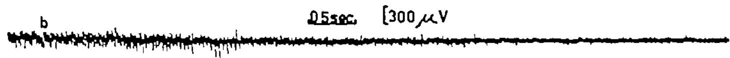


Fig 4 Dystrophia myotonica 3 mg succinylcholine intra-arterially Result (Fig 1 Mechanical effect of about 1·0 seconds duration.

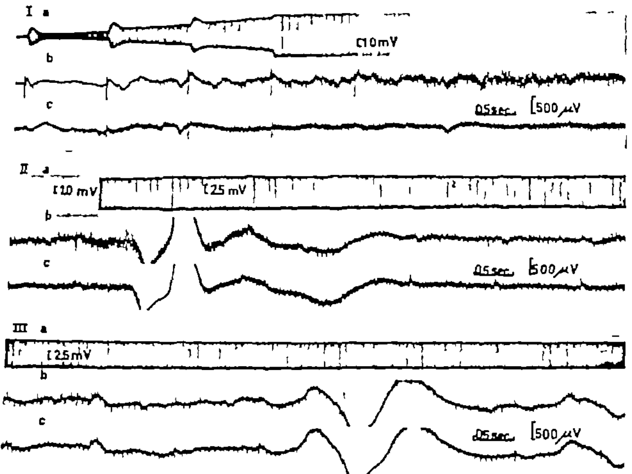


Fig. 5. Dystrophia *myotonica*, 50 mg succinylcholine intravenously. Results as in Fig. 1. The effect of the [illegible] stimulation ceases. Mechanical effect of about 30 second duration.

Injection of a dose as small as 0 3 mg ACh (Fig 2) produced a mechanical effect and, in the hypothenar interfering activity which remained during the whole mechanical response. In the long flexor however only a few action potentials appeared during the response — a circumstance possibly attributable to differences in the supply of the agent to the investigated muscle groups. This reaction pattern of the hypothenar diverged essentially from the 10 mg ACh reaction pattern which differed significantly in activity levels (Fig 1) This difference was less pronounced after doses of 0 3—10 mg

The maximum amplitude of the interfering activity in the hypothenar was generally between 100 and 300 microvolts, and that in the long flexor between 100 and 200 microvolts.

Choline

The effect of Ch on myotonic muscle was essentially the same as that of ACh. The effects of given doses of Ch varied in different patients as was the case with ACh. After injection of 2 mg Ch an interfering activity was registered in the hypothenar but not in the long flexor (Fig. 3) This was also the case after injection of 40 mg These results are probably attributable to disparities in distribution of the agent to the investigated musculature

Succinyldicholine

Each of the 25 injections of SCh was followed by a muscular effect. After injection of large doses (50—160 mg) an increased resistance to insufflation of air

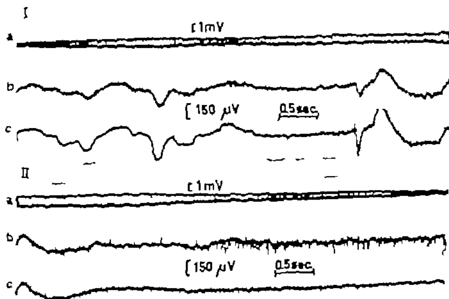


Fig 6. Myotonia congenita, 5 mg. succinyldicholine intra-arterially Earlier in the experiment the patient had received 65 mg succinyldicholine intravenously The electrical activity remains during the regression of the mechanical effect. Result as in Fig 2 a, Mechanical effect of about 15 seconds duration.

into the lungs was noted. Other findings were extension and subsequent flexion of the toes, flexion of the wrist, and accoucheur's position of the hand on the unregistered side.

Intra-arterial doses of 25 mg. and intravenous doses of 50 mg. elicited the reaction illustrated in Figs. 4 and 5. This effect was almost identical with that obtained after 10 mg. ACh except that it was considerably longer in duration.

After intra-arterial injection of 5 mg. SCh in one patient (a woman with m.c.) a mechanical effect and an electrical activity remaining during the whole regression were observed in both the hypothenar and the long flexor (Fig. 6). The response accorded essentially with that obtained after 0.3 mg. ACh.

Thus, on comparing the mechanical effect with the electrical activity it was possible — just as it had been with ACh — to distinguish two different reaction patterns.

The maximum amplitude of the interfering activity both in the hypothenar and in the long flexor was, as a rule between 100 and 200 microvolts.

Using surface electrodes, LANDAU (1952) showed that spontaneous electrical activity is frequently present in myotonic muscle. In order to study the effect of this phenomenon in the present investigations, the circulation in one arm was blocked, on two occasions, with a blood-pressure cuff, and SCh was injected, either intravenously or intra-arterially into the contralateral arm. Only slight electrical activity — or none at all — was registered from the hypothenar of the blocked arm. The registration curve from the other arm, however showed a considerable electrical activity.

Experiments involving registration of action potentials from deep flexors produced essentially the same results.

Fig. 5 shows the results of ulnar nerve stimulation during both progression and regression of the mechanical effect. It is evident that during the latter phase the indirect irritability of the myotonic muscle was considerably reduced. This reduction was observed after injection of SCh as well as after injection of ACh, Ch and C_{10}.

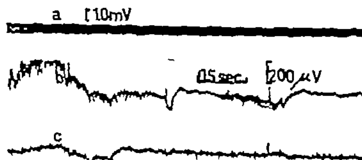


Fig. 7. Dystrophia myotonica, 40 mg. succinylcholine intravenously. Neuromuscular block. Curve b shows showers of potentials after movements of the needle electrode; spontaneous electrical activity.

Injection of a dose as small as 0 5 mg ACh (Fig 2) produced a mechanical effect and, in the hypothenar interfering activity which remained during the whole mechanical response In the long flexor however only a few action potentials appeared during the response — a circumstance possibly attributable to differences in the supply of the agent to the investigated muscle groups. This reaction pattern of the hypothenar diverged essentially from the 10 mg ACh reaction pattern which differed significantly in activity levels (Fig 1) This difference was less pronounced after doses of 0 5—10 mg

The maximum amplitude of the interfering activity in the hypothenar was generally between 100 and 300 microvolts, and that in the long flexor between 100 and 200 microvolts.

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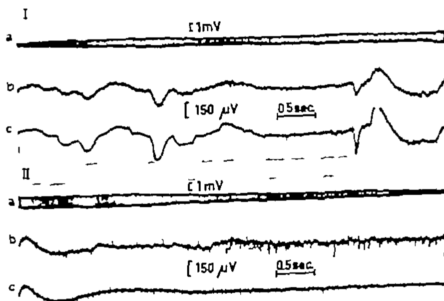


Fig 6. Myotonia congenita, 5 mg succinyldicholine intra-arterially Earlier in the experiment, the patient had received 65 mg succinyldicholine intravenously The electrical activity remains during the regression of the mechanical effect Results as in Fig. 2 a, c. Mechanical effect of about 12 seconds duration.

Experiments on humans involve several difficulties which do not apply to animal experiments. The muscle of an experimental animal can be isolated. The injection can then be made directly into the artery branch which supplies the muscle and the effect can be recorded directly from the muscle. In human subjects, however, it must suffice to inject the agent into one of the major arteries, such as the brachial, whereby the agent is, in consequence, distributed to several muscles. Thus, while electromyographic registration can be performed from single well-defined muscles, the mechanical registration usually represents the combined effect of several muscles.

The stimulatory effects of ACh, Ch, SCh and C_{10} in neuromuscularly healthy subjects with or without anaesthesia have been studied electromyographically by various authors.

After ACh injections into the brachial artery (blocked from circulation) of healthy subjects, Grob *et al.* (1956) observed flexion or fasciculation as well as a burst of muscle action potentials varying from 50 to 100 microvolts recorded via skin electrodes from the hypothenar region. With the aid of needle electrodes used in conjunction with injection in patients with uninterrupted circulation it was found that the amplitude of the potentials in the hypothenar of our myotonia cases varied, as a rule, between 100 and 300 microvolts.

In the experiments of Grob *et al.* (1956 a) there was an interval of 2—5 seconds between the injection and the observed effect. The same interval was usually noted in our experiments.

With intra-arterial Ch injections between 5 and 100 mg, Grob, Johns & Harvey (1956 a) noted a brief period of visible fasciculation which could be recorded electromyographically (personal communication from Johns). In our patients with d.m. not only a mechanical effect, but an electrical interfering activity was recorded after administration of Ch.

The factors responsible for the variations in muscle response after ACh and Ch injections have been discussed by several authors (Acheson *et al.*, 1948; Rowley *et al.*, 1960; Öxndahl, 1962).

Grob *et al.* (1956 b) observed on intra-arterial injections of C_{10} in normals, "a burst of motor activity" registered via needle electrodes, they also noted fasciculations. Our patients with d.m. showed both a mechanical effect and an electrical interfering activity after intravenous, as well as after intra-arterial injections of C_{10}.

After injections of SCh into healthy subjects in doses which gave rise to apnea, Björk & Wåhlin (1958) observed during general anaesthesia, a sparsity of action potentials of varying form and, occasionally, an episode of interfering activity. Fasciculations were also observed by these authors but no accoucheur position of the hand was reported. In our healthy control subject only occasional potentials were registered after SCh injection. All our patients with myotonia showed interfering activity after injections of SCh. After large doses an accoucheur's position of the hand was noted.

By means of simultaneous mechanical and electromyographic registration, it is possible to establish whether or not a

Decamethonium

The responses following injection of C_{10} were closely consistent with those following ACh Ch and SCh An intra arterial dose of *1 mg* resulted in a tracing similar to that in Fig 3 after 2 mg Ch After intravenous injection of 5 mg the tracing corresponded to that in Fig 1 after 10 mg ACh

The mechanical irritability was tested both by percussion and by moving the needle electrode during partial and total neuromuscular block after C_{10} or SCh (*Fig 7*) *On these occasions* a myotonic reaction on percussion and an increased irritability to movements of the needle — often registered as showers of potentials — were recorded

Controls

In the neuromuscularly healthy controls no mechanical effect was observed to follow injections of ACh Ch SCh and C_{10} (Table I) Half the total number of ACh injections however were followed by electrical activity registered as a few action potentials per second. No interfering activity was observed Similar activity was registered after injection of SCh. No electrical activity was, however observed to follow injections of Ch and C_{10} except for one Ch injection (5 mg) after which a few potentials were noted

In the patient with muscle paralysis following a plexus injury ACh gave rise to an appreciable mechanical effect (Table I) as well as an interfering activity The effect of 20 mg ACh is shown in Fig 8 This tracing was similar to those of patients with myotonia (*cf* Fig 1) Injections of up to 80 mg Ch produced electrical interfering activity but no mechanical effect (Table I)

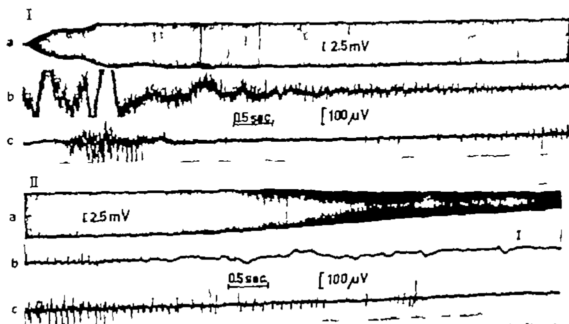


Fig. 8. P ralytic h man musculature after plexus lesion. 20 mg. acetylcholine intra-arterially Results as in Fig I Mechanical effect of bout 18 seconds duration.

Experiments on humans involve several difficulties which do not apply to animal experiments. The muscle of an experimental animal can be isolated. The injection can then be made directly into the artery branch which supplies the muscle and the effect can be recorded directly from the muscle. In human subjects, however it must suffice to inject the agent into one of the major arteries, such as the brachial whereby the agent is, in consequence distributed to several muscles. Thus while electromyographic registration can be performed from single well-defined muscles, the mechanical registration usually represents the combined effect of several muscles.

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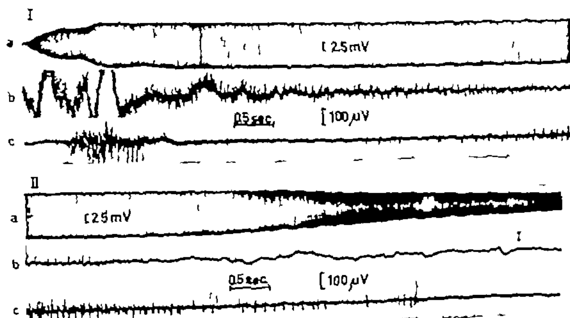


Fig 8. Paralytic human musculature after plexus lesion. 20 mg. acetylcholine intra-arterially Results as in Fig 1 Mechanical effect of about 15 seconds duration.

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A COMPARATIVE STUDY OF CHRONIC NON-OBSTRUCTIVE PYELONEPHRITIS AND RENAL PAPILLARY NECROSIS

By

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Abbreviations and Nomenclature

C_{In}	=	inulin clearance
GFR	=	glomerular filtration rate
M	=	mean value
μEq	=	mikro-equivalents
mEq	=	milli-equivalents
mOsm	=	milli-osmoles
S.D	=	standard deviation
Tm_D	=	maximal tubular transport of diodrast
Tm_{PAH}	=	maximal tubular transport of para aminohippurate

There is some confusion in the literature concerning the use of the terms chronic pyelonephritis and "chronic interstitial nephritis" In the Anglo-Saxon and mostly in the Scandinavian literature the nomenclature favours pyelonephritis irrespective of whether an ascending or a hematogenous infection is postulated. Others maintain that pyelonephritis should be reserved mainly to the obstructive form, wher there is a convincing involvement of th renal pelvis. However the pathways o the bacteria to the kidney still remain tc be established. Experimental hematogenous pyelonephritis has usually been produced only when the ureter is obstructed (86) or the renal parenchyma is dam aged (3) On the other hand ascending pyelonephritis has been produced by injecting bacteria into the urinary bladder even in the absence of urinary tract obstructions (154) Such data make it questionable to use "hematogenous pyelonephritis interstitial nephritis" and "non-obstructive pyelonephritis as sy nonyms, as has often been done. Inter stitial nephritis is also used, when the disease is considered to be abacterial.

For the present series the term "chronic pyelonephritis has been used, and when quoting other authors their nomenclature has been used

Introduction.

Renal papillary necrosis was in earlier years mostly described in pyelonephritis secondary to obstructive uropathy (120, 146) or in pyelonephritis associated with diabetes mellitus (45 87). The disorder was described as a fulminating and usually fatal form of pyelonephritis (9) and the diagnosis was usually not made until the autopsy

During the last decade increasing attention has been drawn to another form of renal papillary necrosis with a chronic, often insidious clinical course. Most reports originate from Switzerland and the Scandinavian countries. There is strong evidence that a relation exists between the incidence of renal papillary necrosis and prolonged and excessive consumption of phenacetin (49a, 54 78, 100 143 150).

Renal papillary necrosis is mostly described as an advanced stage in the so-called "phenacetin nephritis which has been claimed to be an abacterial interstitial nephritis (95 143 149). The histopathologic picture offers, however no pathognomonic features by which phenacetin nephritis can be distinguished with certainty from chronic pyelonephritis. It is also a delicate task to exclude bacterial invasion of the kidneys during the long run of a chronic renal disease. In animal experiments it has not been possible to produce renal damage with phenacetin alone.

The increased number of reports on interstitial nephritis with and without renal papillary necrosis is probably not only due to an increased interest in the disorder The number of cases reported is now so large that a true increase in frequency seems probable. This may be a reflection of the progressively increased consumption of phenacetin-containing drugs (30 113 99 133)

Renal papillary necrosis with a chronic course also exists as a feature in chronic pyelonephritis unassociated with phenacetin consumption (5a, 54) This feature of chronic pyelonephritis has only attracted scanty interest in later years. Thus, it was not even mentioned in the International Symposium on Pyelonephritis held in Detroit in 1959

It was postulated at the beginning of this study that "phenacetin nephropathy" does exist as a separate entity though proof is still lacking. The original aim of this study was to compare some clinical features and functional patterns in chronic non-obstructive pyelonephritis, renal papillary necrosis and "phenacetin nephropathy" (without renal papillary necrosis) This third series was planned to include cases with prolonged phenacetin consumption, renal impairment not attributed to any other renal disease, and absence of urinary tract infection. No such case was found there was always either a history of infection or actual signs of infection. Thus, the study was limited to comparison between two series of cases.

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The final aim of this study was

1 to investigate the relationship between symptoms of infection and consumption of phenacetin in chronic non obstructive pyelonephritis and in renal papillary necrosis. It was expected that the consumption of phenacetin should be larger in the latter series, and that the frequency of urinary tract infections should be lower

2. to analyse the incidence of hypertension in the two series.

The incidence of hypertension is higher in chronic pyelonephritis than in non renal diseases (15 42) and in the general population (10b 46) In "phenacetin nephritis and in renal papillary necrosis, hypertension is often reported to be a rare or infrequent feature, but the findings are contradictory in later publications (49a, 54)

3 to analyse some functional patterns in chronic non-obstructive pyelonephritis and in renal papillary necrosis.

Whether chronic pyelonephritis causes a proportionately greater reduction of tubular than of glomerular function is uncertain Co-existence of obstructive uropathy renal papillary necrosis or other disorders of importance for the tubular function is often impossible to evaluate in earlier published series of pyelonephritis.

The impairment of concentrating capacity reported in phenacetin nephritis" and its relation to early development of renal papillary necrosis need to be investigated. So far in series consisting of renal papillary necrosis exclusively there seems to be a proportionately greater reduction of concentrating capacity than of GFR.

Urinary acidification is the third tubular function to be studied as only few studies in chronic non-obstructive pyelonephritis and none in renal papillary necrosis have been reported.

CHAPTER I

Material.

The material comprises 169 patients, of whom 166 have been treated in the First Medical Department of Sahlgrenska sjukhuset, Göteborg, some time during the years 1958—1961. Three patients were treated in other departments. Several of the patients were seen at the hospital even before 1958. During their first stay in the hospital or during the follow-up study the clinical investigation was supervised by the author and the history was taken or completed by me or collaborating colleagues. 80 patients have been under the care of the author for periods varying from a few months up to five years.

The material was divided into two groups: 75 cases of chronic non-obstructive pyelonephritis and 94 cases of renal papillary necrosis. The selection of the cases was made according to the following criteria: Cases with diabetes mellitus were excluded from the very beginning. Cases with urinary tract obstructions were also excluded, e. g. tumors and "primary" stones. "Primary" stones signify cases in which no known or suspected history of urinary tract infection preceded the stone disease. The material comprises three cases with *one* stone episode each and with urinary tract infections prior to this episode. In the series of renal papillary necrosis there are several patients with transient ureteral obstructions due to passage of sequestered papillae. Here the obstruction was secondary to the renal disease.

Cystoscopi and micturition cystography were usually performed in cases with severe cystitis or when the urogram had shown a widened ureter. They were also performed in patients complaining of stress incontinence after delivery. During the last year the indication for micturition cystography was widened, and it was performed as part of the routine investigation in the majority of new cases of pyelonephritis. If the investigations showed disturbances of the emptying of the bladder or abnormalities of the ureteral orifices, e.g. ureterocele, the patients were excluded from the material. Ureteral reflux was found in some cases, but these were not excluded from the material, since it is uncertain whether the reflux should be considered as primary or secondary to the infection. In one patient the reflux disappeared after long-term treatment with sulfa drugs.

Since disturbances of micturition often occur in elderly women, females

over 65 years of age were excluded. There are similar reasons to exclude elderly men, and since impaired emptying of the bladder is not always noticed in prostatic diseases, the upper age limit for men was set att 55 years in this study

Further cases excluded were those with congenital malformations of the pelvis, the ureter and the lower urinary tract. On the other hand cases with a probable or suspected renal hypoplasia were included because of the difficulty *to differ between hypoplasia with secondary infection and infection with secondary atrophy*

The age and sex distribution in the two series is presented in fig 1 The age at the first investigation during the years 1958—1961 is given The mean age was 47 years in both series. The age distribution was similar in both series, the median age being 49 years in the series of chronic non-obstructive pyelonephritis and 48 years in the series of renal papillary necrosis. The sex distribution is striking Only 11 out of the 169 patients were males, and they all belonged to the series of papillary necrosis.

Number of deaths

In the series of chronic pyelonephritis four patients died during the four year period of this study Three of them died from uremia. The fourth had also uremia, but cerebral haemorrhage was the main cause of death.

In the series of renal papillary necro-

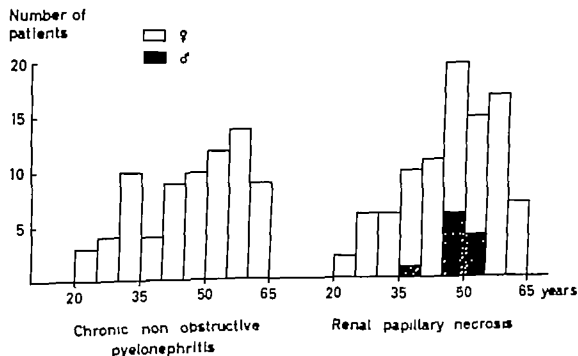


Fig. 1 Age and sex distribution.

Table I

Mode of diagnostics and main cause of death in 16 cases of renal papillary necrosis

Main cause of death	Diagnosis first established by:		
	X-ray	Biopsy of voided papilla	Post-mortem examination
Uremia	5	1	6
Cerebral haemorrhage	2		
Myocardial infarction	1		1

as 16 patients died. Uremia was the main cause of death in 12 of them. Two patients died from cerebral haemorrhage and two from myocardial infarction, and all but one had uremia. In table I are given the mode of first diagnosing the renal disease and the main cause of death in the series of renal papillary necrosis.

Diagnostic criteria.

The following criteria were used for the diagnosis of chronic pyelonephritis.

History of one or several attacks of acute pyelonephritis and/or cystitis. Proven pyuria. Significant bacteriuria. Impairment of renal function. Positive roentgenologic findings. Typical histopathologic findings.

Acute pyelonephritis is characterized by fever pain and tenderness in the loins, bacteriuria, pyuria and often dysuria. Regarding the anamnestic criteria *of acute pyelonephritis*, a history of an episode with these symptoms was accepted, even if the urine had not been examined for bacteria. On the other hand, an attack of *high fever* without local symptoms was not accepted as acute *pyelonephritis* unless a massive pyuria and bacteriuria had been found.

A history of cystitis was accepted only if the patient had been under medical treatment for these symptoms.

In chapter II the criteria used for significant pyuria and bacteriuria are given. The lower limits for normal renal function are also given in that chapter. To exclude transient impairment of renal function, it was required that the impairment should still be demonstrable two months after an acute exacerbation.

The roentgenologic criteria for chronic pyelonephritis, described by Dejdar (25), have essentially been adhered to. As a sharpening of his criteria, it has been required in all cases that there should be changes of several calyces *with flattening of the papillary tips* in one or both kidneys. An example of typical roentgen findings is shown in fig. 2.

The roentgen films of the total material were examined by two roentgen specialists together at the Roentgen Diagnostic Department, Sahlgrenska Sjukhuset. They knew that the patients had an established or suspected clinical diag-

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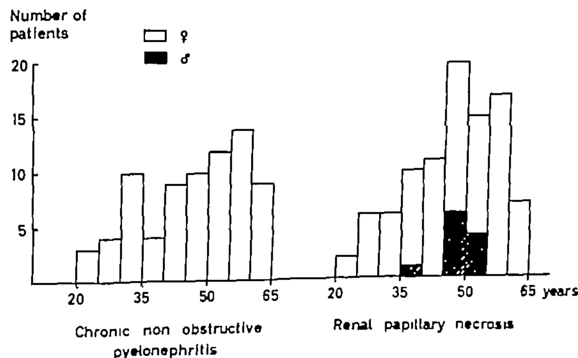


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Fig. 2. Intravenous urography *in a* case of chronic non-obstructive pyelonephritis. Typical changes with dilated calyces, flattened papillary tips and large cortical scars.

The patient was a 43 year old woman with innumerable attacks of acute pyelonephritis (case H. *H. la (53))* Renal Function: endogenous creatinine clearance 87 1/24 hours, concentrating capacity 647 mOsm/kg H_2O and minimum pH 5 18

Fig. 3 Intravenous urography in a case of renal papillary necrosis. Upper pictures were taken before voiding a sequestered papilla from the r gth kidney Only slight changes of the left kidney Lower pictures were taken 14 months later Typical changes with cavities in several papillae of both kidneys. Survey pictures showed no shrinkage of the kidneys.

The patient was a 32 year old woman with excess e phenacetin consumption, repeated ttacks of acute pyelonephritis and of renal colic, when passing sequestered papillae. Renal function shortly after the second investigation: endogenous creatinine 102 1/24 hours, concentrating capacity 540 mOsm/kg H_2O and minimum urine pH 5.53








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nosis of chronic pyelonephritis or renal papillary necrosis, but they were not supplied with any data about the individual case.

To accept the roentgenologic changes as indicative of chronic pyelonephritis, it was required that they should still be demonstrable two months after an acute exacerbation or six months after delivery. Cases with shrinkage and scarring of one or both kidneys and with typical changes of calyces, could be accepted without this interval.

The histopathologic specimens were re-examined by a colleague at the Department of Pathology using the criteria for chronic pyelonephritis, which in detail were described first by Staemmler & Dopheide (144) and Weiss & Parker (159).

Sixty-eight of the 75 patients in the series of chronic pyelonephritis fulfilled at least four of the first five diagnostic criteria. (History of one or several attacks of acute pyelonephritis and/or cystitis. Proven pyuria. Significant bacteriuria. Impairment of renal function. Positive roentgenologic findings.) Among these 68 there were two groups with normal or borderline renal function. In one of the groups there was a small kidney on one side whereas in the other group there was no pronounced asymmetry of the kidney sizes. In the latter cases it was required that there should be repeated urinary tract infections.

Six out of the 7 cases, which fulfilled only two or three criteria, were verified histopathologically. One case with typical roentgenologic changes in a small kidney and without proven bacteriuria, had a history of repeated urinary tract infections.

Histopathologic examination was made in 15 cases altogether: in one by renal biopsy, in ten by nephrectomy or partial nephrectomy and in four cases *post mortem*. Intravenous urography had been performed in all of them except in two post mortem cases. The agreement between histopathologic and urographic findings is shown in table II.

The diagnosis of renal papillary necrosis was based on
Roentgenologic examination and/or histopathologic examination *in vivo* or *post mortem*.

Table II
Agreement between urographic and histopathologic findings in 13 cases of chronic non-obstructive pyelonephritis

Histopathologic examination	Urography positive findings	Urography not judgeable
Needle biopsy	1	
Nephrectomy	5	
Partial nephrectomy	3	
Post mortem	1	1

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282. *Martin Seip* Reticulocyte studies. — 1953 Sw cr 13 —
283 *Lennart Müller* and *Bo Andersson.* Werner's syndrome. — 1953 Sw cr 2.—
284 *Sven Hedlund.* Studies on erythropoiesis and total red cell volume in congestive heart failure — 1953. Sw cr 15 —
285 *Josef Burstein* Myocardial infarction. — 1953 Sw cr 8.—
286 *Erik Hedvall.* Pregnancy and tuberculosis. —1953 Sw cr 10 —
287 *Proceedings of the XXIII Scandinavian congress for internal medicine* held in Oslo from 26th to 28th June 1952 — 1953 Sw cr 9 —
288 *William H Bachrach, B R. Rowen, James L Halsted Herbert Schapera, Walter Holmström* and *Pauline Price* A critical analysis of the criteria for the clinical evaluation of anticholinergic and spasmolytic drugs in gastroenterology — 1954 Sw cr 8.—
289 *Gösta Ekelund.* A case of grave hypertension treated according to Dr S. A. Borgström endocrinological method. — 1954 Sw cr 5.—
290 *S A. Borgström* Endocrine treatment of essential hypertension. — 1954 Sw cr 7 —
291 *Gunnar Birke* and *Lars-Olof Plantin.* Studies on urinary 17 ketosteroids. — 1954 Sw cr 10.—
292. *Bertil von Ahn.* The acute effect of tobacco-smoking and nicotine on the electrocardiogram. — 1954 Sw cr 10.—
293 *Martti Ohela.* Studies on the cholinesterase activity of red cell, plasma and synovial fluid, with special reference to rheumatic diseases. — 1954 Sw cr 7.50.
294 *Olav Refsum* The pathogenesis of Boeck's disease. — 1954 Sw cr 15.—
295 *Samuel Bauch* Nomenclature and morphology of the electrocardiogram. — 1954 Sw cr 3 —
296. *Olof Forssman.* Myocardial infarction and adrenal function. — 1954. Sw cr 13.—
297 *Inga Marie Nilsson* and *Anders Wenckert.* Demonstration of a heparin-like anticoagulant in normal blood. I Human blood. — 1954 Sw cr 15 —
298. *Inga Marie Nilsson.* Demonstration of a heparin-like anticoagulant in normal blood. II Horse blood. — 1954 Sw cr 3 —

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307. *Verhandlungen der vierten Konferenz der internationalen Gesellschaft für biologische Rhythmusforschung* 18.—19. September 1953, Basel. — 1955. Sw. cr. 20.—
308. *Proceedings of the XXIV Scandinavian congress for internal medicine* held in Stockholm from 12th to 14th September 1954. — 1955. Sw. cr. 5.—
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313. *Tage Sundin.* The influence of body posture on the urinary excretion of adrenaline and noradrenaline. — 1956. Sw. cr. 6.—
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262 *Proceedings of the XXII Scandinavian congress for internal medicine* held in Helsingfors from 29th June to 1 July 1950. — 1951. Sw. cr. 6.—
263 *Leslie Ifzelius-Ulm.* Aseptic (non-bacterial) encephalo-meningitides in Gothenburg 1932—1950. — 1951. Sw. cr. 8.—
264 *Ilmar Stenberg.* Studies in renal hypertension. — 1952. Sw. cr. —
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277 *IV congrès international de la médecine d'assurance sur la vie.* Stockholm 8—11 Juin 1953. — 1953. Sw. cr. 40.—
278. *Verhandlungen der dritten Konferenz der internationalen Gesellschaft für biologische Rhythmusforschung* am 30. September und 1. Oktober 1949 Hamburg, Deutschland. — 1953. Sw. cr. 15.—
279 *Bror Axel Lamberg.* Radioactive phosphorus as indicator in a chick assay of thyrotrophic hormone. — 1953. Sw. cr. 8.—
280 *Ragnar Romanus.* Pelvo-spondylitis ossificans in the male (ankylosing spondylitis, morbus Bechterew-Marie-Strümpell) and genito-urinary infection. — 1953. Sw. cr. 36.
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282 *Martin Sep.* Reticulocyte studies. — 1953. Sw. cr. 15.—
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284 *Sven Hedlund.* Studies on erythropoiesis and total red cell volume in [illegible] — 1953. Sw. cr. 15.—
285 *Josef Burstein.* Myocardial infarction. — 1953. Sw. cr. 8.
286 *Erik Hedvall.* Pregnancy and tuberculosis. — 1953. Sw. cr. 10.
287 *Proceedings of the XXIII Scandinavian congress for internal medicine* held in Oslo [illegible] June 1952. — 1953. Sw. cr. 9.—
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298. *Inga Marie Nilsson.* Demonstration of a heparin-like anticoagulant in normal blood. II. [illegible] blood. — 1954. Sw. cr. 3.—

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377. *Sven Lalander*: Sick absence in a Swedish company. A sociomedical study. — 1962. Sw. cr. 20.—
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351. *Gerhard Hägerstrand*. Production of hypercholesterolemia and atherosclerosis in rabbits by feeding different fats without supplementary cholesterol. — 1960. Sw cr 10.—
352. *H. F. West*. Adrenocorticotropins and their use. — 1960. Sw cr 5.—
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356. *Åke Lindgren*. A study of the effect of protracted occupational exposure to carbon monoxide with special reference to the occurrence of so-called chronic carbon monoxide poisoning. — 1960. Sw cr 15.—
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359. *Chr. F. Borchgrevink*. Long term anticoagulant therapy in angina pectoris and myocardial infarction. — 1960. Sw cr 8.—
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363. *Kari Seppälä*. Exfoliative cytology in gastric malignancy. With special reference to the diagnostic significance of nuclear size and mitotic frequency. — 1961. Sw cr 10.—
364. *Oleg Gorbatow*. Die Herzinfarktfrequenz in einem Material der Bevölkerung von Helsinki während der Jahre 1945—1952. — 1961. Sw cr 10.—
365. *Lars Sandberg*. Studies on electrocardiographic changes during exercise tests. 1961. — Sw cr 15.—
366. *Studies on the cardiopulmonary function in sarcoidosis*. Edited by Nils Svanborg. — 1961. Sw cr 17.—
367. *J. F. Heremans, I. H. F. Laurell, L. Mårtensson, M. Th. Heremans, C. B. Laurell, J. Sjöquist* and *J. Waldenström*. Studies on abnormal serum globulins (M-components) in myeloma, macroglobulinemia and related diseases. — 1961. Sw cr 15.— (Out of print.)
368. *Gerhard Dotevall*. Gastric function in diabetes mellitus. A clinical and experimental study with special reference to gastric secretion of acid. — 1961. Sw cr 5.—
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370. *Inge Edler*. Ultrasoundcardiography. — 1961. Sw cr 15.—
371. *Richard Hellström*. Body build, muscular strength, and certain circulatory factors in military personnel. — 1961. Sw cr 10.—
372. *Kim Grander*. Studies on human serum β-lipoproteins, including their protein moiety. — 1961. Sw cr 5.—

373. *F. H. Wallenius:* Balance studies on protein metabolism in normal and uraemic men. — 1962. Sw. cr. 20.—
374. *Ilmari Palva:* Vitamin B_{12} deficiency in fish tapeworm carriers. — 1962. Sw. cr. 10.—
375. *Sven E. Nilsson.* Genetic and constitutional aspects of diabetes mellitus. — 1962. Sw. cr. 10.—
376. *C. H. Brise* and *L. Hallberg.* Iron absorption studies. II. — 1962. Sw. cr. 10.—
377. *Sven Lalander.* Sick absence in a Swedish company. A sociomedical study. — 1962. Sw. cr. 20.—
378. *Gösta Magnusson.* Kidney function studies with ¹³¹I-tagged sodium ortho-iodohippurate. — 1962. Sw. cr. 15.—
379. Haemophilia in Sweden. Part I. By *J. E. Jorpes, B. Blombäck, M. Blombäck, S. Magnusson* and *O. Ramgren.* Part II. By *O. Ramgren, I. M. Nilsson* and *M. Blombäck.* — 1962. Sw. cr. 20.—
380. *M. H. Frick.* Observations on hemodynamic factors and left heart performance in essential hypertension. — 1962. Sw. cr. 10.—
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382. *Hans Bergen.* Studies on the cardiopulmonary function in the post-infectious phase of "atypical" pneumonia. — 1962. Sw. cr. 10.—
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388. *Ulla Bengtsson.* A comparative study of chronic non-obstructive pyelonephritis and renal papillary necrosis. — 1962. Sw. cr. 10.—
389. Myotonic human musculature. Stimulation with depolarizing agents. *G. Örndahl* and *K. Stenberg.* Mechanical registration of the effects of succinylcholine, succinylmonocholine and decamethonium. *I. Peterssén, K. Stenberg* and *G. Örndahl:* Simultaneous mechanical and electromyographic registration. — 1962. Sw. cr. 8.—
390. *Hans Reichard.* Studies on ornithine carbamoyl transferase activity in blood serum. A methodologic, experimental and clinical investigation. — 1962. Sw. cr. 5.—

The roentgen films were examined by two roentgenologists together as described on page 9. The roentgenologic criteria for renal papillary necrosis, described by *Lindvall (80)* were adopted in all details. An example of typical roentgen findings is shown in fig. 3.

The series comprises 94 cases. The diagnosis was made solely on roentgenographic evidence in 64 patients (intravenous urography 63 cases, retrograde pyelography one case). In 30 patients the diagnosis was verified histopathologically. The roentgen findings in these 30 patients are shown in table III. The majority of the patients in this series presented clinical symptoms suggestive of renal papillary necrosis. Gross haematuria was a common feature as pointed out by Mellgren & Redell (89). Attacks of renal colic or dull pains were also frequent in the series of renal papillary necrosis. Transient elevations of serum creatinine ha e on several occasions been much higher than in uncomplicated attacks of acute pyelonephritis.

Besides the cases with examined fragments of papillae some have passed fragments of tissue too disintegrated for histologic identification, and some have given data suggestive of voided papillae. Most of the patients who voided fragments of papillae did so repeatedly, one patient no less than 13 times. A voided papilla of typical appearance is shown in fig. 4. Two cases with detached papillae developed calcified concrements.





Fig. 4. Sequestered papilla.

Discussion.

The relationship 75:94 between the cases of non-obstructive chronic pyelo-

Table III

Agreement between roentgenologic and histopathologic findings in 30 cases of renal papillary necrosis

Histopathologic examination	Urography positiv findings	Urography not judgeable	Plain survey no calcifications
Voided papillae	11	1	
Voided papillae + post mortem	1		
Needle biopsy	1		
Nephrectomy	1		
Post mortem	8	1	6

lonephritis in males is rare, unless there is a primary lesion of the urinary tract.

In a review of 250 cases of renal papillary necrosis reported in the world literature (mainly post-mortem cases), 65 per cent of the patients were females, and 54 per cent of the patients were over 60 years of age (74). In the present series 83 out of 94 patients were females. In clinical materials of renal papillary necrosis the proportion of females to males has been similar to these figures (49a, 54). The only exception from the rule of female prepondérance appeared in the investigation by Nordenfelt & Ringertz (100), which will be discussed in chapter IV.

Reliability of the diagnostic criteria.
Thougt chronic pyelonephritis is a common disease, the clinical diagnosis is often difficult to establish with absolute certainty. With the criteria used in this study several cases were excluded, which in the clinical routine had been handled as cases of chronic pyelonephritis.

As a consequence of the criteria used for the diagnosis of renal papillary necrosis, a technically satisfactory urography was required in every case in both series, unless histopathologic examination disclosed or excluded papillary necrosis. In the latter case only post mortem examination could be accepted. This means that cases with advanced renal impairment had to be excluded from this study unless the diagnosis was proven histopathologically.

Three cases were excluded, which fulfilled the criteria for chronic pyelonephritis, but in addition had a history suggestive of acute glomerulonephritis. Chronic glomerulonephritis has become an infrequent disease in later years. In an autopsy material from the last five years (Malmö) there goes one case of chronic glomerulonephritis on thirteen cases of chronic pyelonephritis according to a preliminary report. Thus, the probability is even smaller that "silent" cases of glomerulonephritis with a superimposed pyelonephritis should be hidden in this series.

It is generally accepted that the clinical diagnosis of chronic pyelonephritis can be made without histopathologic verification, but several authors doubt that the diagnosis of renal papillary necrosis can be made without this verification. In 1960 Lauler et al. (74) made a detailed analysis of 250 cases of renal papillary necrosis collected in the world literature from the first case described by von Friedreich in 1877 (36). They only included cases verified histologically still holding the view that roentgenographic signs are suggestive but not diagnostic. They stressed the hazards of retrograde pyelography and stated furthermore "that intravenous urography should be undertaken with great caution, since most of these patients have rapidly deteriorating renal function".
This rapidly deteriorating course of the disease in earlier reports is probably an important reason why a roentgenologic diagnosis has been difficult or impossible to make. However in Lindvall's (80) and in Hultengren's series (54) as well as in the present one, the renal disease had a slowly progressive course in the great majority of cases. Lindvall has

nephritis and renal papillary necrosis does certainly not reflect the true relationship in incidence between these two types of renal disease in the general population. In later years the general practitioners seem to diagnose and treat cases of uncomplicated pyelonephritis to an increasing extent. Mainly cases resistant to therapy or complicated by haematuria or pains are referred to hospital thus must favour the preponderance of papillary necrosis in a hospital population. Another factor is probably the great interest in the renal effect of phenacetin abuse arisen in the last few years. Thus, there are reasons to believe that renal papillary necrosis is overrepresented in this material.

The relatively large number of cases with renal papillary necrosis does, however demonstrate that this is a frequent disorder The increased number of cases seen and reported in recent years seems to be due partly to better means of diagnosis, but a true increase also seems probable.

The age distribution in the two series is not fully comparable with other published materials of pyelonephritis or renal papillary necrosis because of the selection made and the exclusion of higher ages. The mean age is, however between 40 and 50 years in recent clinical materials of chronic pyelonephritis and of renal papillary necrosis, which include diabetic and obstructive cases (16 42 49a, 54) The relatively low age emphasizes the serious aspect of the disease, especially the variant with renal papillary necrosis. The mortality rate is also considerably higher in this series than in the series of chronic non-obstructive pyelonephritis. This comparison is, however not quite valid since renal papillary necrosis might sometimes be a late feature in chronic non-obstructive pyelonephritis.

In the hospital wards, especially in medical departments, chronic pyelonephritis seems to be a disease that mostly affects females. It is apparent that the female preponderance is most pronounced in the younger age groups and in atrophic or non-obstructive pyelonephritis (56 82 116, 128) Furthermore, acute pyelonephritis is much more common in females (35 158) which might be one explanation, why chronic pyelonephritis is more easily diagnosed in them Asymptomatic bacteriuria is also a more common finding in females (61) Though the clinical diagnosis of chronic pyelonephritis in males might easily be overlooked, this cannot explain the total absence of males in the present material. Serum creatinine is taken routinely in all inpatients, and elevated values cause renal investigations. A large body of patients with arterial hypertension are referred to and closely investigated in the same medical service. These cases are especially screened for signs of pyelonephritis, which should have led to detection of such cases also in younger males, had there been any

In autopsy materials the incidence of chronic pyelonephritis is fairly similar in the two sexes (56 66 116) and micturition disturbances are fairly common in elderly men These facts and the absence of males in the present series lead to the conclusion that chronic pye-

lonephritis in males is rare, unless there is a primary lesion of the urinary tract.

In a review of 250 cases of renal papillary necrosis reported in the world literature (mainly post mortem cases), 65 per cent of the patients were *females*, and 54 per cent of the patients were *over 60 years of age* (74). In the present series 83 out of 94 patients were females. In clinical materials of renal papillary necrosis the proportion of females to males has been similar to these figures (49a, 54). The only exception from the rule of female preponderance appeared in the investigation by Nordenfelt & Ringertz (100) which will be discussed *in chapter IV*.

Reliability of the diagnostic criteria:
Thougt chronic pyelonephritis is a common disease, the clinical diagnosis is often difficult to establish with absolute certainty. With the criteria used in this study several cases were excluded, which in the clinical routine had been handled *as cases of chronic pyelonephritis*.

As a consequence of the criteria used for the diagnosis of renal papillary necrosis, a technically satisfactory urography was required in every case in both series, unless histopathologic examination disclosed or excluded papillary necrosis. *In the latter case only post* mortem examination could be accepted. This means that cases with advanced renal impairment had to be excluded from this study unless the diagnosis was proven histopathologically.

Three cases were excluded, which fulfilled the criteria for chronic pyelonephritis, but in addition had a history suggestive of acute glomerulonephritis. Chronic glomerulonephritis has become an infrequent disease in later years. In an autopsy material *from the last five* years (Malmö) there goes one case of *chronic glomerulonephritis* on thirteen cases of chronic pyelonephritis according to a preliminary report. Thus, the probability is even smaller that "silent" cases of glomerulonephritis with a superimposed pyelonephritis should be hidden in this series.

It is generally accepted that the clinical diagnosis of chronic pyelonephritis can be made without histopathologic verification, but several authors doubt that the diagnosis of renal papillary necrosis can be made without this verification. In 1960 Lauler et al. (74) made a detailed analysis of 250 cases of renal papillary necrosis collected in the world literature from the first case described by von Friedreich in 1877 (36). They only included cases verified histologically still holding the view that roentgenographic *signs are suggestive but not* diagnostic. They stressed the hazards of retrograde pyelography and stated furthermore that intravenous urography should be undertaken with great caution, since most of these patients have rapidly deteriorating renal function. This rapidly deteriorating course of the disease in earlier reports is probably an *important reason, why a roentgenologic* diagnosis has been difficult or *impossible* to make. However in Lind*vall's (80)* and in Hultengren's series (54) as well as in the present one, the renal disease had a slowly progressive course in the great majority of cases. Lindvall has

presented the only exhaustive study of the roentgenographic features in a large material of renal papillary necrosis.

The roentgenologic changes in renal tuberculosis may be similar to those in early renal papillary necrosis. Urine culturing on Löwenstein's medium and inoculation of guinea pig were performed in all cases to rule out tuberculosis. No test was positive.

The roentgen picture of medullary sponge kidney with small changes may resemble unpronounced renal papillary necrosis, but such small changes were not present in this series.

The histopathologic examination is the utmost test of the exactness of the clinical diagnosis. In this material 45 cases in all were examined histopathologically.

The main part of the material was examined roentgenologically. Those cases which were also examined histopathologically are available for judging the reliability of the roentgenologic diagnostics. A requirement for a roentgenologic diagnosis is of course that the renal function is good enough to give a judgeable urography. This requirement was fulfilled in 34 cases of the histologically verified cases (12 cases of chronic non-obstructive pyelonephritis and 22 cases of renal papillary necrosis). There was agreement between roentgenologic and histopathologic findings in all of them. The same comparison was made in seven additional cases — four cases of chronic pyelonephritis and three cases of renal papillary necrosis — excluded from this material because of smaller urinary tract obstructions. Even in these cases there was agreement between roentgenologic and histopathologic findings. On the basis of these results the conclusion is drawn that the roentgenologic diagnosis can be considered reliable also in the rest of the material.

The roentgenologic re-examination of this material has been made as a basis for a correlative study of clinical and roentgenologic features in pyelonephritis.

CHAPTER II

Methods

Urine cultures of clean voided specimens were done in all cases.

Quantitative counts of the urine bacteria were done in 1959 in doubtful cases only, more frequently in 1960 and routinely in 1961. Clean voided specimens were used and refrigerated at 0 to 4° C promptly after collection. Culturing was performed within 24 hours, serial tenfold dilution plate counts being used. In non-quantitative cultures the growth of bacteria was usually estimated as abundant, moderate and sparse.

As a main rule 100,000 bacteria per ml were set as lower limit for significant bacteriuria, according to Kass (60, 61). When judging the figures of quantitative counts, several factors must, however, be taken into consideration (60), such as rate of urine flow, ureteral or local obstruction of urine flow, urine acidity, interval after treatment and time for collection (random or first morning specimen).

Urine culturing on Löwenstein's medium and inoculation of guinea-pig for detection of tubercle bacilli were performed in all cases with renal papillary necrosis and sometimes in other cases.

Urinary sediment.

Centrifuged specimens of urine were used, and ten or more white blood cells per high power field were taken as significant of pyuria. True pyuria is probably present at lower numbers of white blood cells, as indicated by the studies of Wright (168), but a number of ten white blood cells was chosen as a safe limit for the purpose of the present study.

Quantitative sediment examination was performed in a minor part of the material. 3 million white blood cells were taken as significant of pyuria in a 12-hour night urine volume.

Serum creatinine was determined according to the method of Bonsnes & Taussky (11) in the routine control of renal function both in hospitalized patients and in the outpatient clinic.

1.2 mg% has been set as upper normal limit for serum creatinine, since higher values were seldom seen in patients with non-renal disease. The majority of patients with a serum creatinine of 1.3 mg% had a reduced GFR.

The 24-hour "true" endogenous creatinine clearance was used as a clinical measure of GFR (17, 47, 50). The creatinine

was analysed by the method of Loken (after adsorption on Lloyd's reagent) (85) Clearance values are given in litres/24 hours/1 73 m² body surface area. In a normal material in this hospital 107 1/24 hours was the lower limit (M 2 S.D) (55) and the lower normal limit in this study has been set at 110 With increasing age there is a progressive diminution in GFR, as shown by Davies & Shock (23) The reduction is about 20 per cent from 25 to 65 years of age.

The concentrating capacity of the kidney was determined after intramuscular administration of *pitressin tannate in oil* (5 pressure units) according to de Wardener (158) The ampoule was warmed in the hand and well shaken before the administration There were no restrictions in the diet, but the fluid intake was restricted to half a glass of water to each meal. The urine was voided every third hour during the subsequent 24 hours. The osmolality of urine was calculated from the freezing point depression measured with a thermistor and a resistance bridge.

Discussion of the pitressin tannate test

The concentrating capacity after injection of pitressin tannate is usually somewhat lower than after water deprivation for 24—36 hours. De Wardener (157) found no certain difference in maximum specific gravity at advanced tubular damage. Around the level of 1 020 the specific gravity was about 0 002 higher after water deprivation than after pitressin tannate. We found a similar difference in 1958 when both tests were used in a series of 20 patients. In normal subjects Jones & de Wardener (59) found a mean maximum osmolality of 972 after pitressin tannate and 1 118 after 48 hours of water deprivation. Their lowest value after pitressin tannate was 813

The pitressin tannate test is less unpleasant for the patient and does not require the patient's strict cooperation. The pitressin tannate test was combined with a moderate water restriction, as a large amount of water has been shown to reduce the antidiuretic effect. When used in non-acute stages the pitressin tannate test has a good reproducibility The maximum values seldom varied more than 50 mOsm/kg H_2O whether the test was repeated after one week or several months.

800 mOsm/kg H_2O has been set as the lower normal limit for the concentrating capacity when measured by the pitressin tannate test. Like de Wardener we have found that to be an acceptable lower normal limit in non renal disease. However in young healthy people the lower normal limit is probably not below 1000 mOsm/kg H_2O but any chosen limit is bound to be arbitrary in a series with large age differences. Lewis & Alving (77) found in normal men the lower limit of specific gravity after the concentration test of Addis & Shevky (1) to be 1 029 at 20 years and 1 023 at 65 years of age. In our correlation diagram of osmolality and specific gravity (fig. 5) 800 mOsm/kg H_2O corresponds fairly well to a specific gravity of 1 024 As the osmolality is the more physiological measure of urinary con

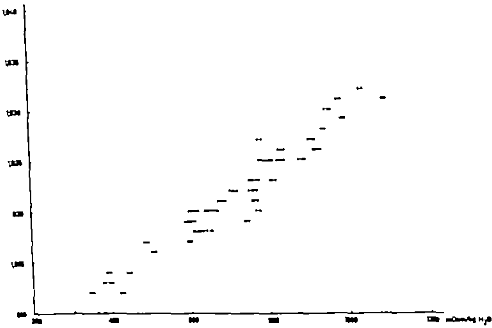


Fig. 5 Correlation of specific gra ity to osmolality

centration, this measurement is to be preferred.

The ability to excrete an acid urine and ammonium was studied after loading with ammonium chloride. The short test described by Wrong & Davies (169) was adopted. Ammonium chloride in a dose of 0.1 g per kg body weight was given orally in gelatin capsules over one hour to avoid gastric irritation. Urine was collected during the subsequent 7 hours. There was no restriction of meals, and water intake varied.

In the first 22 patients it was found that there was no considerable rise of titratable acid and ammonium until the end of the third hour and minimum urine pH was invariably reached during the last four hours of the test. After these findings the test was simplified urine was collected only during the last four hours, divided into two periods. The two control periods before the load were also omitted, only the urine pH at the start being measured. As one-hour periods were practised in the first patients, the mean values of excreted acid and ammonium for two hours had to be determined in these cases, and the mean pH was calculated from the amounts of free hydrogen ions divided by the 2 hour urine flow

Chemical methods

Urine was collected under liquid paraffin. Urine pH was determined with a Radiometer PHM 22p at room tem-

perature titratable acid by titrating a sample to pH 7 4 with 0 05 N NaOH ammonium with the Kjeldahl technique using the destillation apparatus of Kirsten (69) total CO_2 according to the method of Lehmann using Conway s diffusion unit (75)

The error of measurement of pH was S D 0 02

The normal upper limit for minimum pH after NH_4Cl loading has been set at *5 20 which was the mean pH +* 3 S.D in a group of 13 healthy subjects. The range of 3 S.D was used as the age distribution differed from the patient series, only three subjects being over 30 years of age.

The regression line for the normal relationship between ammonium excretion rate and urine pH, as calculated by Wrong & Davies (169) has been used. The healthy subjects in the present study were distributed within the same normal limits (95 per cent range) (Fig 21)

The normal range for the excretion of ammonium and titratable acid are given in table VI

Serum electrolytes were determined by the following methods sodium and potassium by flame photometry chloride by electrometric titration (75) calcium by a photoelectric micro method according to Lehmann (76) phosphorus by the method of Fiske & Subbarrow (34)

Normal ranges in mEq/l for serum electrolytes in the Central Laboratory sodium 139—148 potassium 3 6—5 1 chloride 99—107 calcium 4.3—5.3 phosphorus 1 6—*2 6* and total CO_2 *23—31*

Statistical methods

t test of mean values χ^2 test, when the series were subdivided and regression analyses according to Snedecor (139)

The laboratory analyses of the acidifying tests and most of the concentrating tests were made in the laboratory of the renal unit.

All other laboratory investigations were made as part of the daily routine work in the Laboratory of Bacteriology and in the Central Laboratory

The statistical calculations were carried out at the Institute of Statistics, University of Göteborg.

CHAPTER III

Frequency of Acute Pyelonephritis and Other Urinary Tract Infections.

Thiemich (148) was the first to demonstrate that acute "pyelitis" also involves the renal parenchyma, and sometimes develops into a chronic disease. In the thirties Schoen (128) and Longcope & Winkenwerder (83) and Weiss & Parker (159) gave clear descriptions of the clinical features of bilateral chronic pyelonephritis. They stressed that classic pyelonephritic attacks are often lacking, and later authors (71, 116, 130) have corroborated this observation. It has especially been emphasized that an asymptomatic or insidious course is by far the most common in advanced cases of chronic pyelonephritis (57, 88). Kass (60) and others (20) found that there are symptoms from the lower rather than from the upper urinary tract, and Kass claims that since there are no reliable means for distinguishing "pure" cystitis from cystitis with renal involvement, all patients with urinary tract symptoms should be treated as though the latter were present.

Renal papillary necrosis has in recent years mostly been described as an advanced stage of "phenacetin nephropathy" in which signs of infection are said to be sparse or absent (143, 150).

Present investigation.

Fig. 6 shows the frequency of acute pyelonephritis in the series of chronic non-obstructive pyelonephritis and of renal papillary necrosis. The patients with a positive history of acute pyelonephritis are divided into those with 1—3 bouts and those with more than 3 bouts. The similarity of the percentage distribution in the two series is evident. In the series of chronic pyelonephritis 39 per cent had 1—3 bouts, and 32 per cent had more than 3, compared with 35 per cent in both corresponding groups in the series of renal papillary necrosis.

We have had a general impression that patients with attacks of acute pyelonephritis preserved their renal function better than patients with a more insidious course of the disease. In order to find out if this impression was correct, the patients were divided into four function groups according to the serum creatinine levels, and each group was subdivided according to frequency of acute pyelonephritis (fig. 7). It turns out to be a surprisingly equal distribution of silent cases and cases with a history of acute attacks in all function groups. The same is true also in the

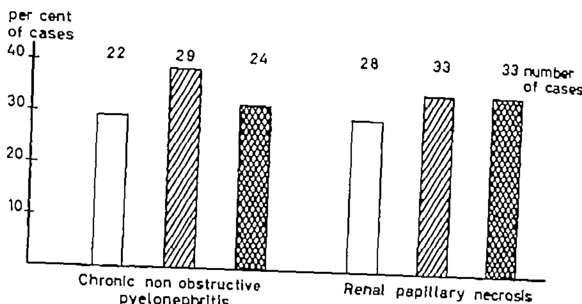


Fig. 6. Frequency of acute pyelonephritis.

☐ no acute pyelonephritis.

☐ 1—3 bouts of acute pyelonephritis.

☐ >3 bouts of acute pyelonphritis.

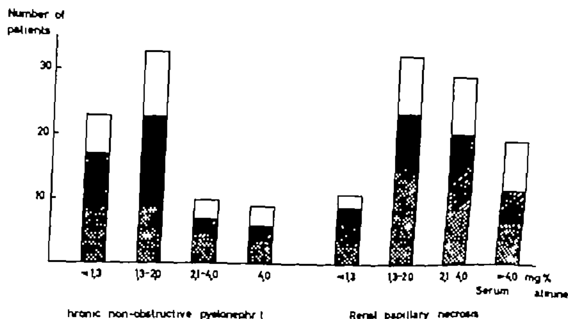


Fig. Frequency of acute pyelonephritis with different degrees of renal impairment

☐ no acute pyelonephritis.

☐ 1—3 bouts of acute pyelonephritis.

☐ >3 bouts of acute pyelonephritis.

series of renal papillary necrosis, though the percentage of advanced renal impairment was higher in this series.

If a dividing line is drawn through the materials at 50 years of age, it turns out that 70 per cent of the younger pa tients, and *71 per cent of the older* presented a history of acute pyelonephritis *in the series of chronic pyelonephritis*, and the corresponding figures were 71 *and 69 per cent in the series of renal* papillary necrosis.

Other kinds of urinary tract infections in this study are: 1. Cystitis, which has been under medical treatment. 2. Subfebrility bacteriuria, pyuria. 3. Silent bacteriuria and pyuria.

In the series of chronic pyelonephritis all but two patients had actual signs or a history of urinary tract infections. The two cases with pyuria only showed hi stopathologic changes typical for chronic pyelonephritis at autopsy.

In the series of papillary necrosis no less than 87 patients had actual signs and/or a history of urinary tract infections. Six patients had only a pyuria. The urine cultures were negative or gave less than 30.000 bacteria per ml. Four of these patients died and showed histopathologic changes typical for chronic *pyelonephritis + papillary necrosis*. One patient had neither bacteriuria nor pyuria.

Table IV shows the occurrence of acute *pyelonephritis* and other kinds of urinary tract infections with and without chronic consumption of phenacetin. The consumption of phenacetin will be analysed in chapter IV. It should only be noted here that in the series of chronic pyelonephritis a history of acute *pyelonephritis was combined with chronic* consumption of phenacetin in 40 per cent, and other urinary tract infections were combined with consumption of phenacetin in 30 per cent. The corresponding figures in the series of renal papillary necrosis were 76 and 81 per cent. Many patients had a history both

Table IV

The interrelationship between *urinary tract infections* and phenacetin consumption

		Chronic non-obstructive pyelonephritis		Renal papillary necrosis	
		Chronic phenacetin consumption			
		−	+	−	+
Acute pyelonephritis	1—3 bouts	21	8	5	28
	> 3 bouts	11	13	11	22
Other urinary tract infections		14	6	4	17
Merely pyuria		2			6
Normal urine findings					1

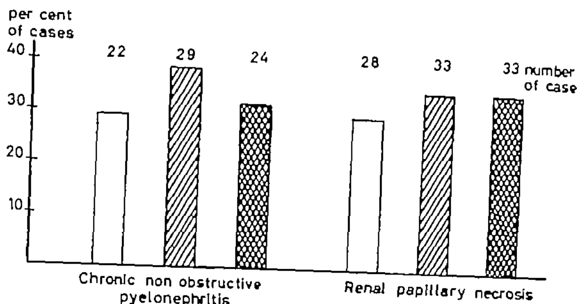


Fig. 6. Frequency of acute pyelonephritis.

□ no acute pyelonephritis.

▨ 1—3 bouts of acute pyelonephritis.

■ >3 bouts of acute pyelonphritis.

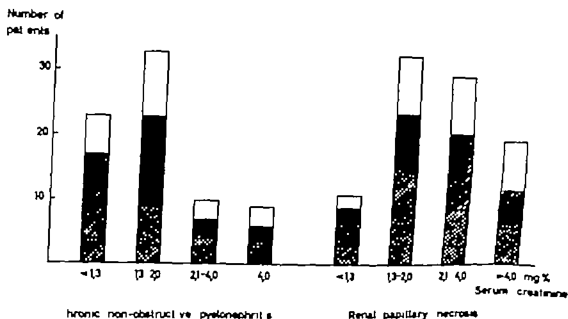


Fig. Frequency of acute pyelonephritis with different degrees of renal impairment

□ no acute pyelonephritis.

▨ 1—3 bouts of acute pyelonephritis.

□ >3 bouts of acute pyelonephritis.

of renal papillary necrosis signs of infection are often found inconspicuous, but in the materials of Lindholm (79) Hultengren (54) and Harvald (49a) the *majority of patients had had pyelonephritic symptoms.*

The incidence of acute pyelonephritis and of other forms of urinary tract infections were strikingly similar in the two series of this material, and provides strong circumstantial evidence, that renal papillary necrosis is just a morphologic variant of chronic pyelonephritis. In urinary tract infections with symptoms only from the bladder and urethra, there is no evidence for bacterial involvement of the kidneys, but renal involvement cannot be ruled out in those cases.

In the six patients, with a pyuria but without a significant bacteriuria and without a history of urinary tract infection the rôle of bacteria in the development of their renal disease is questionable. Guinea pig tests were negative. The pyuria might be explained solely as *a non-specific reaction* to infarcted or sequestered tissue. Several other cases of renal papillary necrosis had a persistent pyuria during or after long term antibacterial treatment, when other signs of infection had disappeared. This fact favours the assumption that pyuria is not always a sign of infection. On the other hand there were two cases in the series of chronic pyelonephritis with pyuria but never proven bacteriuria and no abuse of phenacetin, which post mortem showed typical pyelonephritic changes. Chronic pyelonephritis is a protean disease, and some features may appear with long intervals and therefore be overlooked. The interpretation of the merely pyuric cases is left open.

of acute pyelonephritis and of cystitis, though no account is given of this combination.

During long term treatment or in the follow up after treatment there is one conspicuous difference between the two series. In the series of chronic pyelonephritis, the pyuria most often ran parallel with other signs of activity or disappeared soon after the bacteriuria. In the series of papillary necrosis, however the pyuria often persisted several months or even years after the disappearance of bacteriuria, elevated E. S. R. and other signs of active infection. Moreover this pyuria was often massive with aggregations of white cells, as pointed out by other investigators (74) There were patients with a low quantitative count several months after treatment was withdrawn in spite of other signs of relapsing activity of the pyelonephritic disease. Cultures of voided papillae from two patients showed growth of coliform bacteria, whereas the simultaneous urine cultures were negative.

Gross hematuria occurred much more frequently in the papillonecrotic group 30 cases — than in the pyelonephritic 4 cases. Microscopic hematuria occurred in another 21 cases in the first group and in 11 cases in the latter group

Discussion.

The incidence of a history of acute pyelonephritis is considerably higher in the present material than in an earlier material of chronic pyelonephritis in which the incidence was 46 per cent. (5a) This might be explained by the following facts. The data in the earlier investigation were mainly obtained from routine case records, whereas a penetrating history has been taken from the patients in the present material Furthermore, the patients actual history has been supplemented as far as possible by reviewing their earlier case records from other departments and hospitals during the last 15 years. The results are not comparable with post mortem materials, in which the clinical correlations have been retrospective, nor are they fully comparable with other clinical materials because of the exclusion of higher ages. Jackson et al. (57) found in a material of chronic pyelonephritis, verified by needle biopsies, that two thirds of all the patients had acute exacerbations, whereas among those with the most advanced changes only few gave a history of acute pyelonephritic attacks.

It is possible that an insidious course of the pyelonephritic disease is more common in old patients. Within the age limits of this material of chronic pyelonephritis and renal papillary necrosis there is no significant difference in incidence of acute pyelonephritis between the younger and the older patients.

When comparing the frequencies of acute episodes of pyelonephritis in the different function groups it is obvious that there is no preponderance of insidious cases in the groups with advanced renal lesions. In this respect the present findings do not agree with earlier quoted authors. As pointed out by Jackson et al (57) the degree of renal damage seems to be more related to the duration of the infection, as far as this can be estimated. In materials solely consisting

Spühler & Zollinger in 1953 (143) published a report on chronic interstitial nephritis, in which a possible relationship between excessive consumption of phenacetin and renal disease appeared. Since then these authors, and several other Swiss authors (44 95 133 149 150 170) have furnished convincing data for a relationship between consumption of phenacetin and chronic interstitial nephritis or chronic pyelonephritis. In later years Scandinavian authors (49a, 54 72, 78 100, 123) have confirmed these observations, as have scattered reports from other countries (91 97 125).

Parallel with the increasing number of reports on renal disease with a probable relation to phenacetin, there has been a considerable increase of total consumption of phenacetin in the involved areas (30, 99 113 133).

Zollinger (170), Moeschlin (95) and others (72, 149) have claimed that prolonged consumption of phenacetin causes a genuine interstitial nephritis, which is distinguishable from chronic pyelonephritis, and the names "phenacetin nephritis" and "Saridon nephritis" have been introduced. This is considered to be a non-bacterial interstitial nephritis, involving the kidney in a diffuse manner particularly at the cortico-medullary junction. The diseased kidney has a smooth surface, and even after shrinkage there are no large scars. The interstitial tissue is infiltrated by lymphocytes and plasma cells compressing the tubules which become atrophied, while the glomeruli and vessels are relatively intact. Necroses of the papillae are common.

Reubi (119) and others (125) have claimed that the clinical and pathologic picture in these cases is not distinguishable from chronic pyelonephritis. Reubi also suggests that the headache that has led to the prolonged consumption of phenacetin *is secondary to pyelonephritis.*

Present investigation.

A history of the use of analgetics was taken in all patients, and the use of drugs containing phenacetin was penetrated as far as possible. An estimate of the average daily dose of phenacetin and the duration of the use of the drugs was made. Only the patients themselves were questioned; in a few cases of alcoholism or psychopathia information was also obtained from the relatives.

A daily consumption of 1 g phenacetin during one year has been suggested by Schweingruber (133) as the borderline amount for toxic action. For that reason patients with above *mentioned* minimum consumption were labelled as chronic consumers or abusers of phenacetin in this study It was found, however that also patients who had taken less than 1 g phenacetin daily *often reached* a total consumption of several kg. Therefore patients taking 0.3 up to 1 g daily during at least one year were included in the group of chronic consumers of phenacetin.

Four of the patients in this material had been transferred from a colleague in the Outpatient Clinic of Neurology whom they had consulted because of headache. A history of large consump-

CHAPTER IV

Consumption of Phenacetin

Acetophenetidin (phenacetin) is rapidly metabolized in man The major fraction of the drug is excreted in the urine as conjugated N acetyl p-aminophenol (NAPA) and a very small fraction is converted to p-phenetidin. (18) (Fig 8) It is well established that phenacetin causes blood changes Sulfhemoglobin and small amounts of methemoglobin are formed (127) and when large doses of phenacetin are taken pathologic blood pigment appears in the red cells as Heinz inclusion bodies (95a) hemolytic anemia develops p-phenetidin reduces the life span of the erythrocytes considerably more than phenacetin and NAPA do (114) A dirty gray violet complexion is the most conspicious clinical symptom in chronic abuse.

On the basis of a post mortem series

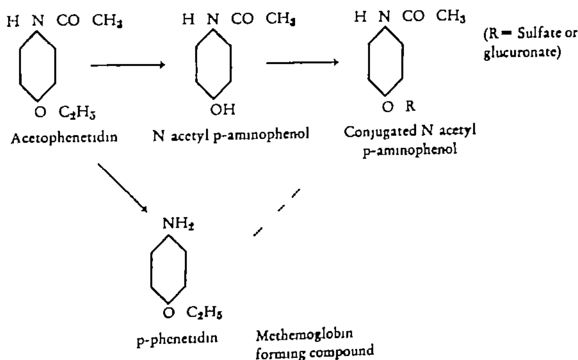


Fig. 8. Metabolism of phenacetin.

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Four of the patients in this material had been transferred from a colleague in the Outpatient Clinic of Neurology whom they had consulted because of headache. A history of large consump-

tion of phenacetin had been obtained and elevated serum creatinine had been found.

The findings in these four patients recently led to an investigation of 35 additional patients from the Outpatient Clinic of Neurology who had been using phenacetin in large doses against headache. Urine concentration test with pitressin tannate, serum creatinine and urinary sediment were used as screening tests. If any test was positive, the patient was submitted to further renal investigation

This separate study was added to the present investigation in order to shed some light on the relationship between renal disease and phenacetin from the phenacetin point.

Results.

In the majority of patients with a large consumption of phenacetin there had been daily consumption. In cases with intermittent consumption the figures are averaged to an estimated daily dose.

The frequency of phenacetin consumption in the pyelonephritic series is shown in fig 9 At least 1 g daily was consumed by 23 per cent of the patients, and the chronic consumers made together 36 per cent. Corresponding data in the papillonecrotic series were 60 per cent and 79 per cent respectively (Fig 9) The difference between the two series is highly significant ($P<0.001$)

The duration of the phenacetin consumption in the two series is given in fig 10 Of the consumers in the pye-

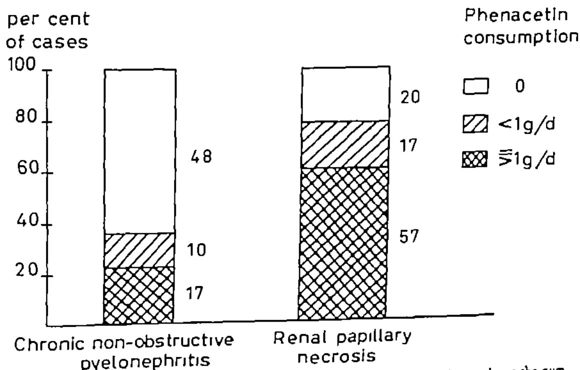


Fig. 9 Frequency of prolonged phenacetin consumption. Figures beside the bars indicate the number of patients.

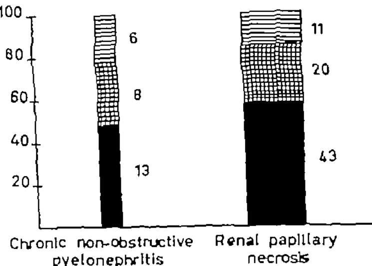


Fig. 10. Duration of phenacetin consumption. Figures beside the bars indicate the number of patients.

lonephritic series, 48 per cent have taken phenacetin more than 10 years, and 22 per cent for 1—5 years. The corresponding figures for the papillonecrotic series are 58 and 15 per cent respectively. Seventeen per cent of all cases in the pyelonephritic series and 46 per cent of all cases in the papillonecrotic series displayed a phenacetin consumtion during more than 10 years. The difference between the two series is highly significant ($P<0.001$).

Fig. 11 shows the relationship in time between the start of phenacetin consumption and the first noted signs of urinary tract infection. In the first series the consumption in 18 per cent of the cases preceded the signs of infection with more than 10 years, and in 56 per cent the signs of infection came first. In the second series the percentage of consumption preceding the symptoms of infection for many years was higher 43 per cent, and the symptoms of infection came first in only 20 per cent. The difference between the two series is significant ($P<0.01$)

Among the patients with a daily consumption of at least 1 g, the majority had taken 1—2 g phenacetin daily but about one third took 3—5 g at least periodically and three exceeded these doses. Several patients started taking phenacetin drugs in early life, and a few patients in both series had taken these drugs for up to 30 years.

All the eleven males in the present material were phenacetin abusers, and in all of them the phenacetin consumption preceded the signs of infection.

tion of phenacetin had been obtained, and elevated serum creatinine had been found.

The findings in these four patients recently led to an investigation of 35 additional patients from the Outpatient Clinic of Neurology who had been using phenacetin in large doses against headache. Urine concentration test with pitressin tannate, serum creatinine and urinary sediment were used as screening tests. If any test was positive, the patient was submitted to further renal investigation.

This separate study was added to the present investigation in order to shed some light on the relationship between renal disease and phenacetin from the phenacetin point.

Results.

In the majority of patients with a large consumption of phenacetin there had been daily consumption. In cases with intermittent consumption the figures are averaged to an estimated daily dose.

The frequency of phenacetin consumption in the pyelonephritic series is shown in fig. 9. At least 1 g daily was consumed by 23 per cent of the patients, and the chronic consumers made together 36 per cent. Corresponding data in the papillonecrotic series were 60 per cent and 79 per cent respectively (Fig. 9). The difference between the two series is highly significant ($P<0.001$).

The duration of the phenacetin consumption in the two series is given in fig. 10. Of the consumers in the pye-

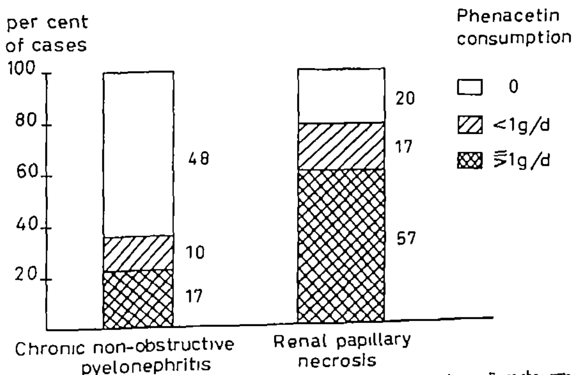


Fig. 9. Frequency of prolonged phenacetin consumption. Figures beside the bars indicate the number of patients.

diagnosed in 9 out of 26 females and in 2 out of 13 males. Three women had an advanced renal damage with a serum creatinine above 3 mg%. Two additional women had an impaired concent rating capacity but in the absence of other signs no renal diagnosis was made.

Discussion.

The possibility to obtain reliable data on the use of phenacetin seems to have diminished during later years, probably due to the increasing public information about the toxicity of phenacetin. Nowadays there is often a defensive attitude when the history is taken at the hospital. Patients who answered the same questions a couple of years ago now tend to understate their earlier consumption. Thus, it is to be supposed that the magnitude of the phenacetin use has been understated in several cases as indicated by a few controlled cases. Furthermore, figures dating many years back are bound to be unreliable. It therefore seemed appropriate to divide the patients with a chronic use of phenacetin only into two groups: those with a daily dose of phenacetin below 1 g and those with a dose of 1 g or more, which has earlier been suggested as the borderline toxic dose. It is, however probable that at an already established renal impairment a smaller dose of phenacetin may be toxic.

The very high incidence of excessive phenacetin consumption in the present series of renal papillary necrosis is in accordance with reports of earlier investigators (49a, 54 78). The incidence of phenacetin consumption was of considerable magnitude also in the pyelonephritic series, and this finding seems to agree with several reports, though the disease is often classified as chronic interstitial nephritis by other authors.

It has been widely discussed whether consumption of phenacetin should be considered as primary or secondary to chronic pyelonephritis. In the present pyelonephritic series 56 per cent of the consumption can be labelled as secondary or coincidental to the pyelonephritis, and in the papillonecrotic series 20 per cent can be labelled so. With an increasing number of years of excessive phenacetin consumption preceding the first noted signs of infection the probability increases that phenacetin is the primary factor and when the consumption for decades preceded the signs of infection it seems reasonable to postulate that the phenacetin should be the primary factor

Headache was the major cause in starting the consumption of phenacetin, but the drug has also been taken against tiredness and many kinds of discomfort. In three patients the headache had been severe enough to cause neurosurgical exploration. Three patients dated their consumption back to a head trauma and two patients to a viral encephalitis. On the whole there was a great variety of headache histories which also favors the assumption of phenacetin as the primary factor in several cases. The same assumption applies to some cases, in which other disorders than headache (bronchial asthma, rheumatoid arthritis) were the cause of phenacetin consumption.

Though it is indicated that phenacetin

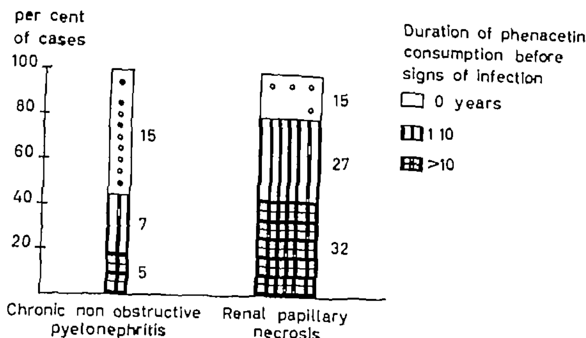


Fig. 11 Duration of phenacetin consumption before noted signs of urinary tract infections. Figures beside the bars indicate number of patients

Among 80 per cent of the patients the drug of choice was the so-called "strong headache powder' which until February 1961 could be obtained without prescription. The powder contains 0.5 g phenacetin, 0 5 g phenazone and 0 1 g caffeine. Some patients used so-called weak headache powders containing 0 3 g phenacetin and the remainder used phenacetin-containing drugs prescribed by doctors.

The findings in the 39 patients from the Outpatient Clinic of Neurology are shown in table V Renal disease was

Table V

Findings in 26 female and 13 male phenacetin abusers from the Outpatient Clinic of Neurology

	♀	♂
Pyelonephritis chron.	3	
Pyelonephritis chron. + nephrolithiasis	1	
Renal papillary necrosis with signs of infection	4	1
Renal papillary necrosis with pyuria and without bacteriuria	1	1
Impaired concentrating capacity normal urine findings and normal urography	2	
Normal findings	15	11

which came first, the bacteria or the phenacetin, once the kidney is diseased, excessive phenacetin consumption frequently causes renal papillary necrosis.

The mode of action of phenacetin on the renal parenchyma is, however still obscure. Hemolysis by itself does not cause interstitial nephritis (94). The following possibilities have been suggested: a direct toxic action of phenacetin or its metabolites (149) or of impurities of the compounds (49b); a toxic action of altered hemoglobins (95b) or of renal tissue hypoxia (72)

A noteworthy fact in the present study is that all eleven males were consumers of excessive amounts of phenacetin, and in all of them did the phenacetin consumption precede the signs of infection. To the former conclusion that chronic pyelonephritis in males is rare unless there are lesions of the urinary tract could be added: and unless there is prolonged consumption of phenacetin. Interesting in this connection is the post mortem series of Nordenfelt & Ringertz (100). Of 38 patients (30 men and 8 women) from a small town, who died in uremia, 27 men and 3 women had been abusers of phenacetin. 22 of the men had been workers in a small-arms factory where it had become a habit to take phenacetin compounds to keep pace with the piece-work. The average consumption of phenacetin in this town was 54 g per head and year and in the neighbouring town 23.6 g compared with 5.3 5.3 6.0, and 8.5 g in four other towns (43).

Otherwise abuse of phenacetin seems to be considerably more frequent in women than in men (44 49a, 54 72, 78, 149) This is probably one of the explanations for the overwhelming female preponderance in the present material. As it is indicated that bacterial invasion of the kidneys is a necessary factor to cause morphologic damage, a female preponderance should, anyhow be expected, even in a population with a phenacetin use of equal magnitude in the two sexes. The number of males in the neurological material of phenacetin consumers is, however too small to shed light on this question, but positive renal findings in 2 of 13 males compared with 11 of 26 females are suggestive that the above mentioned assumption is valid.

Phenacetin is usually taken in compounds containing two or three other drugs. 80 per cent of the patients in this material used powders containing also phenazone. No investigation is known on the possible nephrotoxic effect of this drug. None of the patients had, however used drugs containing phenazone and not phenacetin, though phenazone -caffeine is not infrequently used against bronchial asthma. The three patients in this material with bronchial asthma had used compounds with phenacetin. Clausen & Harvald (19) found in short-term studies that salicylates provoke a greater increase of erythrocytes and leucocytes in the urinary sediment than does pure phenacetin. This is believed to be due to a non-specific effect, but the finding should initiate further investigation. If salicylates had a relation to renal disease it should be expected that patients with chronic use of

in a large number of cases is the primary factor no proof has been found for the suggestion that phenacetin can be the only factor for development of interstitial nephritis. As reported in Chapter III the frequency of urinary tract infections in the papillonecrotic series was very similar to that in the pyelonephritic series. Furthermore, there was no reverse relationship between the frequency of urinary tract infections and phenacetin consumption (Table IV)

Since urinary tract infection is a main criterion for the diagnosis of chronic pyelonephritis, and since renal papillary necrosis is bound to be a *locus minoris resistentiae* for infections, it is reasonable *to question*, if the existence of a non bacterial interstitial nephritis caused by phenacetin can be discussed from the data in this material. However in reality all cases *from* the same period originally diagnosed as "phenacetin nephropathy in the absence of signs of infection have been included in this material During the follow up or in penetrating the past history signs of infection have appeared.

In some of the Swiss publications on phenacetin nephritis" several cases had pyuria, but few or no data were given about urine cultures (44 95 143) Neither these studies nor reports from other places have shown any convincing data that phenacetin alone can produce an interstitial nephritis. Furthermore, there is no clear-cut pathologic picture by which "phenacetin nephritis can be distinguished from chronic pyelonephritis or interstitial nephritis unassociated with phenacetin (78 119 125) Spühler (142) now considers that phenacetin toxicity *per se does* not cause interstitial nephritis, but kidneys exposed to phenacetin are less capable of resisting infections, even by bacteria of low virulence. Similar views have been maintained by other authors during later years (44 150)

Experimental data correspond to clinical experience. Thus, it has not been possible to produce morphologic renal damage by feeding animals with large doses of phenacetin (119 147) Thölen et al (149) produced renal damage in mice, but there was probably a coincidental spontaneous infection with *Closiella muris* which can cause similar changes. Miescher et al. (93) showed that only if phenacetin fed rabbits were exposed to pathogenic bacteria did they develop renal lesions, and these were of the same type as in acute pyelonephritis. Nor did exposition to bacteria alone suffice to cause renal disease. On the other hand Keller at al (65) have not been able to produce interstitial nephritis with phenacetin and bacteria by similar methods. Lately Eisalo & Talanti (29) have given a report on interstitial nephritis produced in rats by feeding 100 mg phenacetin or NAPA daily during one month It is uncertain if spontaneous infection can be ruled out, as bacteriologic cultures were not performed. They also found that the activity of some enzymes disappeared from the renal tubuli.

At present it may be concluded from clinical and experimental data that prolonged consumption of phenacetin makes the kidney susceptible to infection It can also be stated that regardless of

CHAPTER V

Hypertension

Longcope & Winkenwerder (82, 83) and Weiss & Parker (159) were the first to draw attention to the relationship between pyelonephritis and hypertension.

Later a relationship between chronic pyelonephritis and hypertension has been denied by some (4) and considered as a mere coincidence by others (39). The overwhelming majority of investigators have, however found the incidence of hypertension considerably higher in patients with chronic pyelonephritis than in the general population (10b, 46) and in patients with non-renal disease (15 42)

In the so-called phenacetin nephropathy which has a high frequency of papillary necrosis, hypertension has been found infrequent and usually not appearing until the renal damage is far advanced (44 125, 143). In later reports on renal papillary necrosis exclusively the incidence of hypertension has varied considerably (49a, 54 78, 79)

Genetic factors play an important rôle for the development of hypertension and must be taken into account, when studying the relationship between renal disease and hypertension.

Present investigation.

During the hospital stay blood pressure was usually measured several times, and in the two wards where most of the patients were examined, the blood pressure was measured every day The diastolic value was taken as the figure recorded on disappearance of the pulse sound. As a rule the values reported were the mean diastolic pressure for the first three days in hospital, the pressure at admittance being excluded. In patients treated with antihypertensive drugs it was necessary to discontinue the treatment temporarily or to trace their natural blood pressure back to the pretreatment time. If the patients were febrile during the hospital stay the blood pressures from the follow up in the out patient clinic are reported. The pressures were measured after 15—20 minutes in the recumbent position. Blood pressures from frankly uremic or terminal phases are not recorded in the diagrams, except in three cases, in which no earlier values were available. Questioning on the family occurrence of hypertension was made in all cases.

A diastolic blood pressure of 100 mm Hg has arbitrarily been set as upper limit for normotension.

salicylates should be represented in the present material. Especially patients with rheumatoid arthritis should be represented. There were only two such patients in this material and they both took phenacetin-containing compounds.

A positive family history of hypertension was present in 30 per cent of the pyelonephritic series (in 43 per cent of the hypertensives) and in 32 per cent of the papillonecrotic series (in 47 per cent of the hypertensives). The incidence of hypertension in patients with a positive family history was 68 per cent in the pyelonephritic series and 53 per cent in the papillonecrotic series. In patients without a positive family history the corresponding figures were 38 and 28 per cent respectively.

When analysing the blood pressures of the three function groups, it is evident that the mean values of diastolic blood pressure increased with renal impairment in both series: mean diastolic pressure 95 → 102 → 112 mm Hg in the pyelonephritic series and 82 → 95 → 102 mm Hg in the papillonecrotic series. The differences between the groups with the lowest and the ones with the highest serum creatinine are significant. ($P < 0.05$ in the pyelonephritic series, $P < 0.01$ in the papillonecrotic series). The incidence of hypertension in the three function groups was 36, 47 and 63 per cent in the pyelonephritic series and 17, 28 and 56 per cent in the papillonecrotic series.

The mean diastolic blood pressure was higher in the pyelonephritic groups than in the corresponding papillonecrotic groups. In the first and second function groups several pyelonephritic cases had a blood pressure up to 140 mm Hg even without a positive family history of hypertension, whereas no case with necrotic papillae had a diastolic blood pressure above 110 mm Hg unless there was a positive family history of hypertension. One of the two hypertensive patients with papillary necrosis in the first function group had a positive family history and in the other patient the family history was unknown. Six additional cases with unknown family history are evenly scattered in the material.

The spread of values is too great and the number of cases within each function group is too small to give a significant difference between pyelonephritic and papillonecrotic cases within each group. When the total series are compared, the blood pressure is significantly lower in the papillonecrotic series ($P < 0.05$).

Four patients in the pyelonephritic series had malignant hypertension classified according to the degree of retinopathy (Keith-Wagener grade IV) (64) which means 11 per cent of the hypertensive cases in this series. In the papillonecrotic series two patients had malignant hypertension which, however, did not develop until in the terminal phase, and at autopsy they both turned out to have a renal artery stenosis. Most patients in the two series with a diastolic blood pressure of 120 or more and not too far advanced renal impairment — serum creatinine below 3 mg% — have been submitted to renal aortography and have not shown signs of renal artery stenosis.

In a control series of essential hypertension, 26 cases, the incidence of a positive family history of hypertension was 73 per cent which is considerably higher

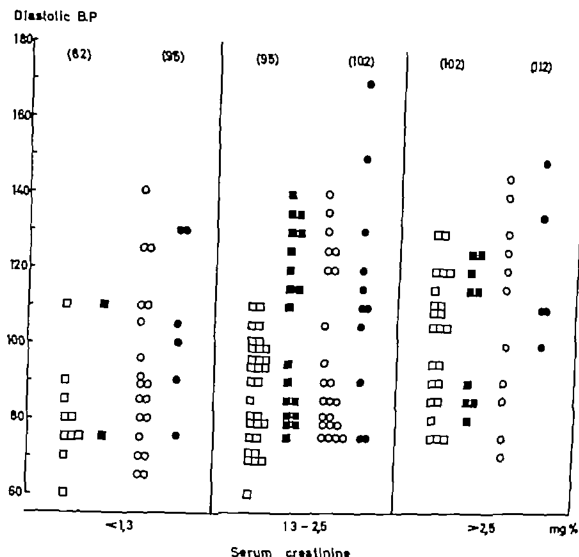


Fig 1. Diastolic blood pressure at different levels of renal function. Each individual is represented by one dot. Figures within parenthesis indicate mean diastolic pressures.

○ Chronic non-obstructive pyelonephritis without family history of hypertension.

● Chronic non-obstructive pyelonephritis with positive family history of hypertension.

□ Renal papillary necrosis without family history of hypertension.

■ Renal papillary necrosis with positive family history of hypertension

Diastolic blood pressure in relation to renal damage is shown in fig 12 The serum creatinine level was used as indicator of the degree of renal damage The two series have been divided into three function groups one with serum creatinine values below 1.3 mg%, one with creatinine between 1 3 and 2 5 mg% and one above 2.5 mg%.

Results.

The incidence of hypertension was 47 per cent in the pyelonephritic series and 36 per cent in the papillonecrotic series.

A positive family history of hypertension was present in 30 per cent of the pyelonephritic series (in 43 per cent of the hypertensives) and in 32 per cent of the papillonecrotic series (in 47 per cent of the hypertensives). The incidence of hypertension in patients with a positive family history was 68 per cent in the pyelonephritic series and 53 per cent in the papillonecrotic series. In patients without a positive family history the corresponding figures were 38 and 28 per cent respectively

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In a control series of essential hypertension, 26 cases, the incidence of a positive family history of hypertension was 73 per cent which is considerably higher

than the incidence in the hypertensive groups of the pyelonephritic and papillonecrotic series. In the series of essential hypertension the upper age limit was 65 years and the mean age 50 years.

Discussion.

The 47 per cent incidence of hypertension in the present series of chronic pyelonephritis is in agreement with the earlier confirmed relationship between hypertension and pyelonephritis. Brod (15) found the incidence of hypertension four times as high in chronic pyelonephritis as in chronic cholecystitis. Grieble & Jackson (42) found the same difference between chronic pyelonephritis and bronchiectasis. In the general population the incidence of hypertension does not exceed 15 per cent (10b 46). In chronic pyelonephritis the incidence has varied from 22 to 70 per cent (5a, 12, 15 71 82 159) and the great spread of the results is probably explained by the different selection and differences in the definition of hypertension. Kleeman et al (71) found a significantly higher incidence of hypertension in atrophic cases than in non atrophic and obstructive cases in spite of a higher mean age in the latter group

The 36 per cent incidence of hypertension in the papillonecrotic series is almost identical with the incidence (37 per cent) in Hultengren's material (54). On the other hand Harvald (49a) found only three cases with hypertension in a clinical material of 66 papillonecrotic patients. Other authors have also found a low incidence of hypertension in renal papillary necrosis or in interstitial nephritis with a high frequency of papillary necrosis (44 95b, 143). In none of the reported series have criteria for the recording of blood pressures been given. In the present investigation it was observed that the blood pressure often fell during febrile periods and in uremic and terminal stages, and therefore pressure values from those periods were excluded. The opposite course, a terminal rise of the blood pressure was less frequent. Kleeman et al (71) found that the incidence of hypertension was greater in clinical series of chronic pyelonephritis than in series diagnosed post mortem and concluded "that the hypertension may decrease somewhat in the terminal phase." Thus, in this respect, it seems difficult to compare the present material with post mortem series, in which probably terminal pressures have been recorded. Uehlinger (150) noticed cases classified as normotensives having a heart enlargement at autopsy

The irregular association of chronic pyelonephritis with hypertension is a well known fact (63). Some cases develop hypertension before signs of renal insufficiency whereas others remain normotensive until death.

It has been shown in the present material that the mean diastolic blood pressure rises with increasing renal impairment. The comparison between the three function groups is independent of the age factor the age distribution being similar in the three groups.

Brod (15) also found an increasing frequency of hypertension in pyelonephritis with increasing renal impairment (measured as GFR and concentrating

capacity). Kleeman et al. (71), using the same parameters as in the present study found no significant correlation between the serum creatinine and the diastolic blood pressure, though their atrophic cases of pyelonephritis had a higher incidence of hypertension than their non-atrophic cases.

When comparing the present pyelonephritic and papillonecrotic series it is apparent that hypertension develops later in renal papillary necrosis than in chronic pyelonephritis. There is a somewhat lower incidence of hypertension even at an advanced renal damage in patients with papillary necrosis. Age distribution is similar and hereditary predisposition for hypertension can be considered of similar magnitude in both series. The comparison is consequently not invalidated by these two factors. However the difference in blood pressures (incidence of hypertension 11 per cent and mean diastolic pressure 7 mm Hg) between the total series does probably not reflect the true relationship in this respect between chronic non-obstructive pyelonephritis and renal papillary necrosis, since the frequency of cases with advanced renal impairment was greater in the series of papillary necrosis. In two series with equal distribution of renal impairment the differences in percentage of hypertension and in mean diastolic blood pressure would probably be greater as indicated by the numerically greater but non-significant differences in the subgroups.

Six initially normotensive patients from each series have developed hypertension during the follow up period. A diastolic blood pressure of 105 mm Hg was reached in the pyelonephritic group at serum creatinine values between 1.2 and 1.7 mg°/o in five cases and around 2.2 mg°/o in one case. In the papillonecrotic cases the same blood pressure was reached at the following values 1.6—2.3 mg°/o in four cases and 3.5—4.0 mg°/o in two cases. Another three patients with renal papillary necrosis demonstrated an opposite course. From an earlier established hypertension they have become normotensive (diastolic blood pressures 110 — 130 → 80 mm Hg, 110 → 85 mm Hg, 115 → 85 mm Hg) at a moderate degree of renal damage and in a satisfactory general condition.

The higher incidence of hypertension in pyelonephritic patients with a family history of hypertension is of similar magnitude as that found by Brod (15). Cruz-Coke (21) found that the hereditary data in pyelonephritic hypertension are often equivalent to those found in essential hypertension. In the present material the incidence of a family history of hypertension considerably separates not only the normotensive patients from the hypertensives but also the latter from the patients with essential hypertension. A family history was present in 73 per cent of the patients with essential hypertension which agrees very well with the 75 per cent found by Platt (111, 112) and the 68 per cent found by O'Hare et al. (103).

The hereditary factor alone does consequently not explain the incidence of hypertension in chronic pyelonephritis. There must also exist a direct causal re-

lationship between chronic pyelonephritis and hypertension as claimed by several investigators, but the mechanism of this relationship still remains to be established

Weiss & Parker (159) demonstrated a proliferative endarteritis in atrophic pyelonephritis and concluded that this vascular lesion was due to the inflammation. In later years Kincaid Smith (67) has beautifully demonstrated similar vascular lesions. Weiss & Parker and Kincaid Smith have proposed that renal ischemia secondary to the endarteritic process should be the cause of hypertension associated with chronic pyelonephritis Most investigators, among them Kimmelstiel (66) have found proliferative vascular changes in chronic pyelonephritis but consider them to be non specific and impossible to differentiate from arterio-and arteriolosclerosis. Brod (15) as well as Kleeman at al (71) observed normotensive cases with a pronounced endarteritis, but Kleeman et al usually found that the endarteritis was extensive, when the hypertension was severe

Katz et al (62) have published a study which suggests that the renin mechanism is involved in the hypertension of pyelonephritis.

Most investigators have been unable to produce hypertension in experimental pyelonephritis. Spitznagel & Schroeder (141) are the only ones who have noted elevated blood pressure in rat pyelonephritis with obstructed ureters, and Vivaldi et al (154) have succeeded in producing hypertension in non-obstructive pyelonephritis. The latter investigators claim that a chronic active pyelonephritis has not been clearly demonstrated in earlier experimental models but rather healed lesions.

The necessity of activity in the chronic pyelonephritis for development of hypertension is not supported by clinical experience (63 118) It has also been observed in this material that hypertension sometimes develops years after the disappearance of signs of infection

Conversely Woods (167) has shown that rats with hypertension induced by desoxycorticosterone acetate and saline exhibit increased susceptibility to pyelonephritis. Shapiro (135) has shown that experimental hypertension in rats is intensified by production of pyelonephritis. Merriam Sommers & Smithwick (90) have examined a large biopsy material obtained during sympathectomy in hypertensive patients, clinically diagnosed as essential hypertension. Of these patients 13.5 per cent had pyelonephritic changes, and these patients exhibited a more severe hypertensive disease with the same degree of arteriolosclerosis than patients without pyelonephritis.

In accordance with these findings the incidence of malignant hypertension is relatively high in published materials of chronic pyelonephritis. Brod (15) found an incidence of 15 per cent and Kleeman et al (71) found approximately 20 per cent of malignant cases in pyelonephritic hypertension. The incidence was 11 per cent in the present series. On comparison less than 2 per cent of all hypertensive patients will have malignant hypertension (2 68) Saphir &

Taylor (124) stated that the great majority of their cases of malignant hypertension were due to chronic pyelonephritis. Other investigators have usually found chronic pyelonephritis in about 20 per cent of *malignant hypertension* (68, 71 159). Björk et al. (10a) found 28 cases of chronic pyelonephritis in a material of 191 cases of malignant hypertension collected from five Swedish hospitals, including this medical department. In addition there were 11 cases of malformed kidneys, i. a. hypoplastic kidneys.

Active treatment of hypertension might prevent the development of malignant stages, but this factor is difficult to evaluate in different series.

It might be speculated that pyelonephritic patients with hypertension and a normal total function should have a small kidney on one side. In the first function group there are also eight cases with one kidney of considerably reduced size, less than 10×4 cm on X-ray and the other kidney of normal or supernormal size. Four of these cases were, however normotensive, and one of these normotensives had furthermore a positive family history of hypertension.

Why cases with renal papillary necrosis have a lower incidence of hypertension than cases with chronic pyelonephritis is unknown. As the cases with papillary necrosis in fact have a chronic pyelonephritis, one explanation might be that the necrosis *per se* has some protective property against hypertension. Muirhead et al. (98a+b) showed in some interesting experiments that explanted renal medulla protected against accelerated renoprival hypertension, and extract of medulla prevented the development of renoprival hypertension in dogs. Explants or extracts of renal cortex did not have any of these properties.

Salt losing might be an alternative explanation of the lower incidence of hypertension in renal papillary necrosis. Fend (32) has shown that pyelonephritic patients are potential salt losers which become manifest during osmotic diuresis (glucose load) The reason to expect a salt-losing mechanism in renal papillary necrosis is greater since Hilger et al. (52) have shown that sodium reabsorption takes places also in the collecting ducts. In *an earlier study* (5b) it was found that no pyelonephritic patients with hyponatremia (15 cases) had a diastolic blood pressure above 100 mm Hg regardless of their renal function. Nowadays we rarely see pyelonephritic patients on unwarranted salt restriction. In the present material serum sodium and chloride were normal in the clinical steady state. This does, of course, not exclude the mechanism discussed above.

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Most investigators have been unable to produce hypertension in experimental pyelonephritis. Spitznagel & Schroeder (141) are the only ones who have noted elevated blood pressure in rat pyelonephritis with obstructed ureters, and Vivaldi et al. (154) have succeeded in producing hypertension in non-obstructive pyelonephritis. The latter investigators claim that a chronic active pyelonephritis has not been clearly demonstrated in earlier experimental models but rather healed lesions.

The necessity of activity in the chronic pyelonephritis for development of hypertension is not supported by clinical experience (63 118) It has also been observed in this material that hypertension sometimes develops years after the disappearance of signs of infection

Conversely Woods (167) has shown that rats with hypertension induced by desoxycorticosterone acetate and saline exhibit increased susceptibility to pyelonephritis. Shapiro (135) has shown that experimental hypertension in rats is intensified by production of pyelonephritis. Merriam Sommers & Smithwick (90) have examined a large biopsy material obtained during sympathectomy in hypertensive patients, clinically diagnosed as essential hypertension. Of these patients 13.5 per cent had pyelonephritic changes, and these patients exhibited a more severe hypertensive disease with the same degree of arteriolosclerosis than patients without pyelonephritis.

In accordance with these findings the incidence of malignant hypertension is relatively high in published materials of chronic pyelonephritis. Brod (15) found an incidence of 15 per cent, and Kleeman et al (71) found approximately 20 per cent of malignant cases in pyelonephritic hypertension. The incidence was 11 per cent in the present series. On comparison less than 2 per cent of all hypertensive patients will have malignant hypertension (2, 68) Saphir &

of the glomerular filtrate is reabsorbed proximally by an isosmotic process (73 156). During antidiuresis the fluid becomes isosmotic during the passage through the distal tubule and hyperosmotic in the collecting ducts (40, 165).

In 1951 Hargitay Kuhn and Wirz put forward the hypothesis that the loop of Henle acts as a hairpin counter current multiplier of the osmotic pressure. The hypothesis was based partly on mathematical treatment and model experiments (48) and partly on cryoscopy of kidneys slices, showing increasing osmotic concentrations towards the tip of the papilla (166) The principle of the countercurrent theory is demonstrated in fig. 14

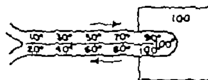


Fig. 14 A countercurrent exchange system. A pipe with water enters an oven with the temperature of 100°C. The incoming water is heated by the outgoing water and the heat in the oven is conserved. (From Schmidt-Nielsen (134)).

In 1958 Gottschalk & Mylle (40) succeeded in puncturing the bend of the thin segment in the golden hamster They found that the urine at this point had the same osmotic pressure as the urine in the collecting ducts and the blood in the vasa recta at the same level, thereby producing evidence for the countercurrent mechanism.

The details of this mechanism in the kidney are not yet established. Wirz (164) and Berliner et. al. (7) have suggested that the ascending limb of the loop of Henle has a specific function, that of active transport of sodium. Sodium chloride is believed to be transported out of the relatively water impermeable ascending limb into the medullary interstitium. The urine in the thin descending limb comes into osmotic equilibrium with the interstitial fluid by the diffusion of water out from and of solutes into the lumen, thus raising the osmolality of the urine presented to the ascending limb. In this way an increasing osmotic pressure is established towards the tip of the papilla (fig. 15).

Instead of hyperosmotic reabsorption of sodium chloride in the loop of Henle a secretion of water into the loop might be postulated to explain the hypotonicity in the early part of the distal tubule. To differentiate between these two possible mechanisms Gottschalk (40) induced osmotic diuresis with mannitol, which is non reabsorbable, and with sodium chloride. When comparable urine flows were achieved, the hypotonicity of the fluid in the early part of the distal tubule was considerably more pronounced, when sodium chloride was the loading solute. This is considered a strong evidence for the hyperosmotic reabsorption mechanism. Sodium chloride is the only physiological solute present in sufficient quantity to explain the degree of achieved hypotonicity

Ljungberg (81) demonstrated already in 1947 a progressive concentration of chloride in the medulla of rabbit kidney exceeding that in any other tissue. The physiological significance of this finding was not evident at that time, but the high chloride concentration fits with

CHAPTER VI

Renal Function

As the main interest in this chapter will be focused on the renal functions localized to the papilla and the distal tubule short reviews will be given of the concentrating mechanism and the urinary acidification.

The concentrating mechanism

Only in mammals and birds is a renal papilla developed which can produce a hyperosmotic urine The papilla contains three parallel structures the loop of Henle, the collecting ducts and the vasa recta (fig 13) These three structures make a functional unit with the capacity of producing a hyperosmotic urine. In the human kidney nephrons arising in the outer cortex turn in the cortex, whereas in nephrons starting from the juxta medullary glomeruli the loop descends for a variable distance into the medulla (106) The short loops are about seven times as numerous as the long ones. In *Psammomys* all loops reach the tip of the papilla (140) and the maximum urine concentration is 6000 mOsm/kg H_2O (102) compared to 1200—1400 in man (117)

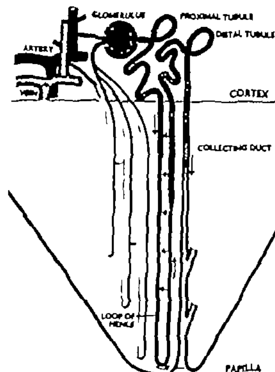


Fig. 13 Functional unit of the renal papilla. (Reproduced from Scholander (129))

The concentrating mechanism of the kidney has been extensively studied during the last two decades. It has been shown in amphibian and mammalian kidney that proximal tubular fluid is isosmotic with plasma, and fluid in the early part of the distal tubule is hypoosmotic under all conditions (40 156 164) In the mammal 65—80 per cent

neys. Vasopressin has also been shown to increase the equivalent pore radius of kidney slices from *Necturus* (160)

The vasa recta participate in the concentrating mechanism (163) Solute diffuses into and water probably out of their descending limb and in the ascending limb these movements go into the opposite directions, thus minimizing the loss of solute from the medulla. (Fig. 15)

Urea also plays a role in the concentrating mechanism. (153) Passive diffusion from the collecting ducts has been postulated, but the mode of transport over the limbs of the loop of Henle is unknown.

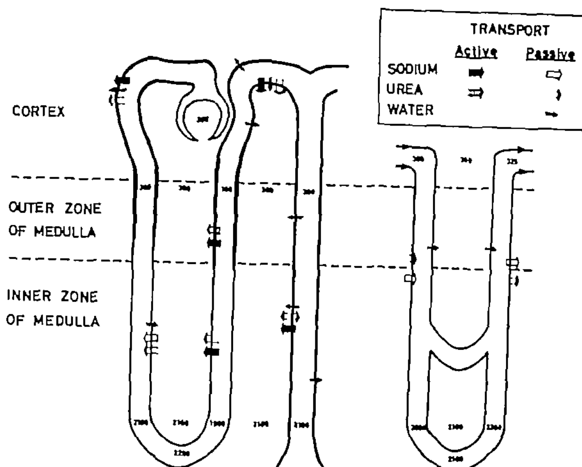


Fig. 15 Diagram depicting the countercurrent mechanism as it is believed to operate in a nephron with a long loop and in the vasa recta. The numbers represent hypothetic osmolality values. No quantitative significance is to be attached to the number of arrows and only net movements are indicated. As is the case with the vascular loops, all loops of Henle do not reach the tip of the papilla, and hence the fluid in them does not become as concentrated as that of the final urine but only as concentrated as the medullary interstitial fluid at the same level. The active sodium transport by the epithelium of the collecting duct is based on the work of Hilger et al. (52). (Slightly modified from Gottschalk & Mylle (40)).

the present theory for the counter current mechanism

It has been shown that in the presence of antidiuretic hormone, the urine becomes isosmotic in the last half of the distal tubule, and the urine osmolality in the collecting ducts increases until it is the same as in the medullary loops (40 165) The conclusion is that antidiuretic hormone makes the distal tubule and the collecting ducts freely permeable to water which then diffuses along the established concentration gradients. It has also been suggested that the antidiuretic hormone has an additional effect on the loop of Henle and/or the medullary blood flow (165)

Further support for the site of action of antidiuretic hormone has been given by Darmady at al (22) by localizing ^{131}I labelled pitressin to the distal tubules and to the collecting ducts in rat kid

med within one month after passage of a papilla are included here. The obstruction of the urinary tract was usually a matter of some hours. Cases who got a persistent hydronephrosis are included in the material but excluded from the diagrams of function. 36 cases of essential hypertension (all females) were chosen as a control material, being worked up along the same lines and during the same period.

Among the cases submitted to function studies 19 pyelonephritic cases and 15 papillonecrotic cases were hypertensive.

Results.

In the series of chronic pyelonephritis no dissociation between concentrating capacity and GFR could be demonstrated (fig. 16). In the series of renal papillary necrosis the concentrating capacity was reduced relatively more than the GFR. Even cases with a normal GFR could not produce a urine osmolality above 720 mOsm/kg H_2O (fig. 17). The difference between the slopes of

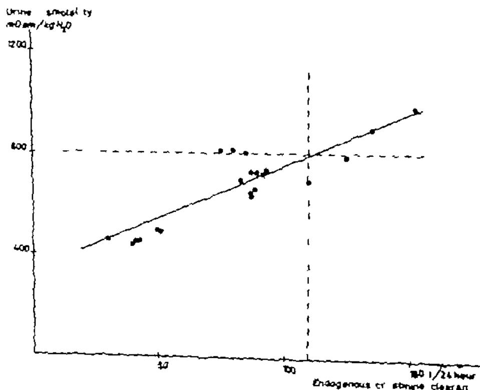


Fig. 16. Relationship of concentrating capacity to GFR in chronic non-obstructive pyelonephritis. Each dot represents one individual. Dotted lines indicate normal limits. Regression line $Y_X = 339 + 4.33X$.

The relationship between concentrating capacity and gfr

Typical for the chronic pyelonephritic kidney is the wide variety of histopathologic changes. As the inflammation attacks the tubules and the interstitial tissue first and most severely great interest has been focused on the question whether a glomerulotubular imbalance of function does exit or not. The results in some studies (16 70 115) suggest that the concentrating mechanism may be specifically damaged in chronic pyelonephritis but in other studies (13 26, 116) a proportionate reduction of GFR and concentrating capacity has been found. The impairment of concentration is then considered to be attributed to a relative osmotic diuresis (13 137)

In renal papillary necrosis the morphologic reasons to expect a specific concentrating defect are stronger than in other kinds of renal damage. Hypo- or isostenuria has been described as a common feature even in early cases (49a, 54 143)

Present investigation.

Serum creatinine was determined in all patients in the routine control of renal function. "True endogenous creatinine" clearence was used as a clinical measure of GFR, and pitressin tannate test was adopted for the estimate of concentrating capacity These tests were not performed in patients with advanced renal impairment (serum creatinine above 4 mg%)

The renal function values given below were obtained during afebrile periods. Serum sodium and chloride were within normal range. The total serum CO_2 was sometimes decreased, but never below 17 mEq/litre. At advanced renal impairment, the serum potassium was sometimes at the upper or lower limit of the normal range. Patients with arterial hypertension, who had recently been treated with chlorothiazide or its derivatives sometimes had a serum potassium at the lower normal limit Usually patients with a tendency to decreased serum potassium were supplied with potassium chloride. No test was performed under chlorothiazide treatment. In order to avoid the transient impairment of renal function caused by attacks of acute pyelonephritis, all tests performed within one month after such attacks were excluded. The majority of the values derive from follow up studies, when the patients were admitted to hospital for a few days. Among the patients with renal papillary necrosis no tests perfor

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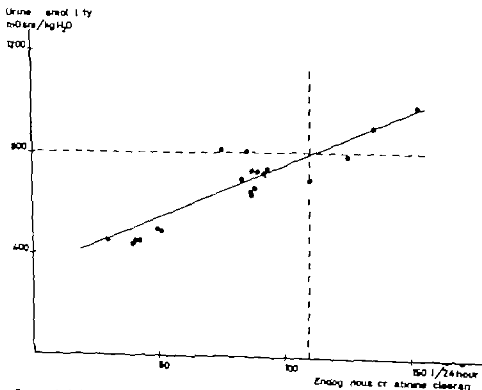


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the regression lines in the two series is statistically significant ($P<0.001$). The regression lines converge with decreasing renal impairment and intersect at an endogenous creatinine clearance of 17 1/24 hours.

In the series of essential hypertension the GFR was reduced at an earlier stage than the concentrating capacity (fig. 18). There was only one case with an endogenous creatinine clearance less than 70 1/24 hours. Above this level the concentrating capacity is significantly higher than in the corresponding range of GFR (70—155 1/24 hours) in the series of chronic pyelonephritis ($P<0.001$)

Discussion.

The aim of this study has been to compare GFR and concentrating capacity in chronic non-obstructive pyelonephritis and in renal papillary necrosis. It was therefore necessary to exclude all conditions which are known or suspected to affect these two renal functions.

In acute pyelonephritis Raaschou (115), Brod (15) and Winberg (161) have found a marked depression of concentrating capacity at normal or slightly depressed GFR. Winberg also found that the concentrating capacity was not normalized until 4—6 weeks after acute pyelonephritic attacks in infants and children. In patients with chronic pyelonephritis we have found that even a slight attack of acute pyelonephritis reduces the concentrating capacity but the GFR is less affected or even unchanged. Two patients regained their ordinary concentrating capacity of 500—600 mOsm/kg H_2O four weeks after one or two severe febrile attacks. In two other patients with less impaired function full recovery occurred after five to seven weeks. Some cases establish a steady state on a new level or may never reach any steady state. In this study one month was taken as a limit to exclude most of the transient impairment from acute exacerbations.

In hydronephrosis the predominance of tubular damage is striking. Winberg (162) and Berlyne (8) have demonstrated a proportionately greater depression of concentrating capacity than of GFR, even in the absence of infection. Jaenike & Bray (58) have recorded the same functional pattern in non-infected acute urinary tract obstructions.

Potassium deficiency may cause a dissociation between GFR and concentrating capacity. Smith & Lasater (138) showed that polydipsia and polyuria occur after a few days of experimental potassium depletion in dogs. Schwartz & Relman (131) recorded a greater reduction of maximum specific gravity than of GFR in a patient with a total estimated deficit of 500 mEq potassium. Hydropic degeneration of tubular cells has been described as characteristic of potassium deficiency. The early damage is predominantly localized to the collecting ducts (104). In the present study a serum potassium within normal range has been considered enough to exclude potassium depletion as a cause of tubular damage.

Hypercalcemia may also cause tubular damage and hyposthenuria (38). Serum calcium and phosphate were deter-

U ine osmolality
mOsm/kg H_2O

1200
800
400

50
100
150 l/24hours
E dogenous creatinine clearance

Fig. 17 Relationship of concentrating capacity to GFR in renal papillary necrosis. Each dot represents one indi dual. Dotted lines indicate normal limits. Regression line: $Y_X = 371 + 2.11\ X$.

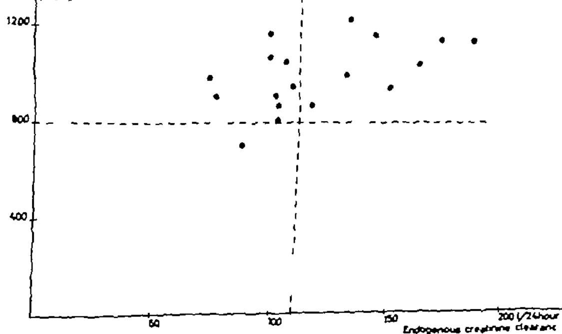


Fig. 18. Relationship of concentrati g capacity to GFR in essential hypertension. Each dot represents one individual. Dotted lines indic te normal lim ts.

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mined in several patients with hypertension and in all cases with calcified papillary necrosis, and the values were always within normal limits.

The finding of a proportionate reduction of GFR and concentrating capacity in the present series of chronic pyelonephritis does not agree with the results in an earlier series (5a) The concentrating capacity seemed then to be proportionately more reduced than GFR. Two factors — inclusion of cases in acute stages and cases of renal papillary necrosis — might explain the difference in the relationship between GFR and concentrating capacity in the earlier study and the present one, as well as the greater spread of values in the earlier series.

In 1943 Raaschou (115) demonstrated a marked dissociation between urea clearance and concentrating capacity in a series of patients with both acute and chronic pyelonephritis. Cases of hydronephrosis and/or obstructive urinary disease were included In his monograph on chronic pyelonephritis Raaschou (116) could no longer demonstrate any dissociation between GFR (estimated as inulin and urea clearance) and concentrating capacity No data were given about the 20 patients submitted to this correlative study

On the other hand Raaschou (116) like Edvall (27) and Kleeman et al. (71) found that GFR is preserved to a greater extent than proximal tubulator function (Tm_D Tm_{PAH}) The question remains which rôle the above mentioned factors have played for the results. Michie & Michie (92) who excluded cases of hydronephrosis, and Jackson et al. (57) found a proportionate reduction of GFR and Tm_{PAH} Bricker et al. (13) found in experimental pyelonephritis in dogs, that the relation between GFR and concentrating capacity was normal.

Brod (16) uses the dissociation between GFR and concentrating capacity as one of the main criteria for the clinical diagnosis of chronic pyelonephritis. He found that the regression line correlating GFR and concentrating capacity was closer to the X axis (GFR) in chronic pyelonephritis than in chronic glomerulonephritis, which in its turn gave a regression line closer to the x axis than did vascular nephrosclerosis.

Brod's material was not a selected non-obstructive material. It seems probable that a large material of chronic pyelonephritis should also contain cases of renal papillary necrosis.

Kleeman and associates (70 71) also claim that a specific concentrating defect exists in chronic pyelonephritis. The values of osmolality after pitressin were lower than would be predicted from the relative osmotic diuresis per nephron C_{In} was used as an estimate of functioning renal mass. Only one of their 14 cases of chronic pyelonephritis had a serum creatinine below 3.5 mg%, and the mean value was 8.2. C_{In} values ranged between 4.5 and 23 8 ml/min At such distortion of the renal anatomy it must be difficult to establish a functional pattern of any disease. Their investigations in patients with chronic glomerular nephritis and other types of chro-

nic renal failure gave the same results. This similarity of functional pattern in advanced renal failure disregarding etiology is in accordance with the findings in the present investigation. The difference in relationship of concentrating capacity to GFR between the two series disappears, when the renal impairment is advanced.

The finding of a specific concentrating defect in the series of renal papillary necrosis agrees with earlier reports and fits with the morphologic damage. In Hultengren's study (54) of renal papillary necrosis the concentrating capacity seems to be more reduced than in the present study. However Hultengren collected urine for only 12 hours after pitressin tannate compared with 24 hours in the present study. The maximum osmolality was often not reached until the second 12-hour period.

The relationship between GFR and concentrating capacity in essential hypertension seems to agree fairly well with Brod's findings (16) and is in accordance with the morphologic changes. The urine flow was somewhat lower in the patients with essential hypertension than in the patients with pyelonephritis and necrosis of the papillae who often had a diuresis between 1.5—2.5 litres/24 hours. Some patients exhibited an obligatory polyuria. In patients with an iatrogenic or voluntary polyuria the water intake was usually reduced the days before the test.

The 19 hypertensive cases in the series of chronic pyelonephritis and the 15 hypertensive cases in the series of renal papillary necrosis are, however, evenly scattered among the other cases in the function diagrams and seem not to influence the relationship between GFR and concentrating capacity.

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Studies on renal acidifying capacity

Several investigators have found that the urine pH in "general renal failure is often lower than in normal subjects, and that the diseased kidney is able to *excrete urine of maximal acidity* (14 51 132, 169) others (33 121) have not been able to confirm these findings. Most investigators have found an impaired excretion of ammonium in renal *failure, including chronic pyelonephritis* (51 71 132, 169).

No study of acidifying capacity in renal papillary necrosis has up to now been published.

Present investigation.

The ability to excrete an acid urine and ammonium was studied after loading with ammonium chloride. The short test described by Wrong & Davies (169) was adopted (see under Methods).

48 patients were included in this investigation, 20 from the series of chronic non-obstructive pyelonephritis and 28 from the series of renal papillary necrosis.

The criteria for the clinical conditions at the time of this test *were the same as* those used for the clearance and the concentrating test. At least one month should have elapsed after acute exacerbation or urinary obstruction. The serum electrolytes were within normal range except in 10 cases with a total CO_2 between 17 and 23 mEq/l (fig. 22). Most of the patients had a negative urine culture or less than 100 bacteria/ml. *Proteus* and *staphylococcus* infections were totally excluded. In six patients there was a growth of 1.000 or more coliform bacteria/ml.

As controls healthy laboratory personnel and medical students, nine females and four males, aged 19 to 48 were also investigated.

Results.

The patients with chronic non-obstructive pyelonephritis maintained the ability to excrete an acid urine even at an advanced reduction of GFR (fig. 19). They all produced a normal or nearly normal minimum pH. Most of the patients with renal papillary necrosis on the other hand, were unable to excrete urine of normal minimum pH, even at a slight or moderate reduction of the GFR (fig. 20). This difference between the two series is statistically *significant* ($P<0.001$).

Before the acid load there was no difference in urine pH between the two series.

The *relationship between* excretion of

The urinary acidification

The acid base regulation by the kidney is accomplished by tubular reabsorption of bicarbonate and elimination of excess anions as titratable buffer acid or in combination with ammonium ions. Since the works of Pitts and his collaborators (107 108 110) during the fourties it has been a generally accepted view that the underlying mechanism is a tubular secretion of hydrogen ions. It is indicated that hydrogen ions formed within the tubular cells (and potassium (6)) are exchanged for sodium ions in the tubular urine. The maximum hydrogen ion gradient which the tubular epithelium can establish between blood and urine is about 800 to 1 (110)

Ammonia is formed within the tubular cells and diffuses into the tubular urine, where it combines with hydrogen ion to form ammonium. Under acidosis more hydrogen ion is excreted bound to ammonia than as titratable acid (126)

The excretion of ammonium is determined by at least three factors availability of ammonia precursors (84 136) enzyme activity (24) and urine pH (105 107) In normal subjects the formation of ammonia reaches its maximum after about four days of acid loading (122) There is a reverse relationship between the rate of ammonium excretion and the urine pH In acute changes of acid-base balance the logarithm of the rate of ammonium excretion has been demonstrated to be a linear function of pH (145 169)

The localization of urinary acidification in amphibian and mammalian kidneys has been studied by means of micropuncture or stop-flow techniques. Most investigators have localized the changes of urine pH to the distal tubule (96 109) which also is the site, where ammonia is added to the urine (109 155) However recent studies indicate that at least in some conditions a significant acidification occurs in the proximal tubule (37) Ullrich and his associates (151 152) have found a fall in pH in the collecting ducts of hamsters, using polyethylene catheters threaded up from the pelvis. They also found an accumulation of ammonium and potassium and removal of sodium in this segment, indicating that the functions of the distal tubule extend down into the collecting ducts. Gottschalk et al. (41) have supported these findings in studies on rats. The greatest fall in pH appeared to occur in the collecting ducts in the non-diuretic state, when a low rate of secretion of hydrogen ions is enough to give a considerable change of pH

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As controls healthy laboratory personnel and medical students, nine females and four males, aged 19 to 48 were also investigated.

Results.

The patients with chronic non-obstructive pyelonephritis maintained the ability to excrete an acid urine even at an advanced reduction of GFR (fig. 19) They all produced a normal or nearly normal minimum pH. Most of the patients with renal papillary necrosis, on the other hand, were unable to excrete urine of normal minimum pH, even at a slight or moderate reduction of the GFR (fig. 20) This difference between the two series is statistically significant ($P<0.001$)

Before the acid load there was no difference in urine pH between the two series.

The relationship between excretion of

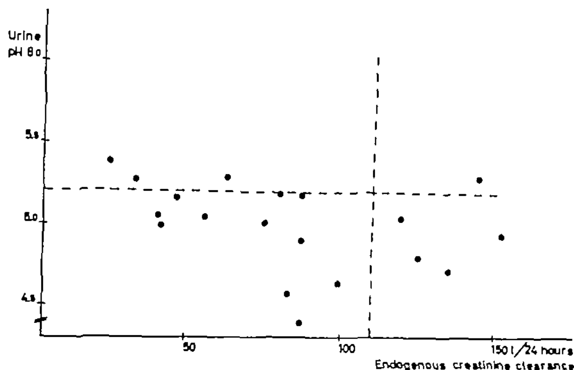


Fig. 19 Relationship of minimum urine pH to GFR in chronic non-obstructive pyelonephritis. Each dot represents one individual. Dotted lines indicate normals limits.

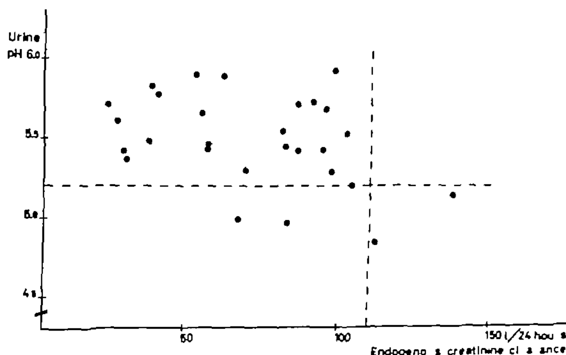
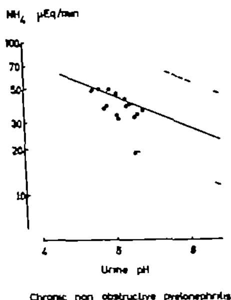
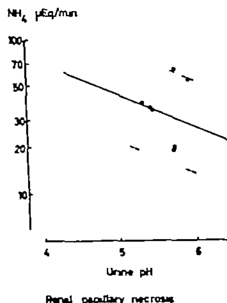


Fig. 20. Relationship of minimum urine pH to GFR in renal papillary necrosis. Each dot epresents one indi idual. Dotted lines indicate normal limits.





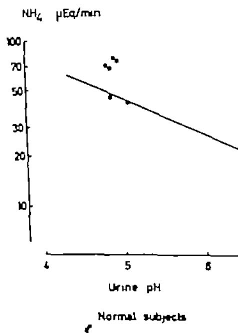


Fig. 21. Relationship of ammonium excretion rate to minimum urine pH. Each dot represents one individual. Normal regression lines $\hat{Y}$ = 2.89 — 0.259 x, where $\hat{Y}$ = log NH_4^+ and x = pH (according to Wrong et Davies) (169). Dotted lines indicate 95 per cent range.

Urine pH 6.0

5.5

5.0

4.5

50

100

150 l/24 hours

Endogenous creatinine clearance

Fig 19 Relationship of minimum urine pH to GFR in chronic non-obstructive pyelonephritis. Each dot represents one individual. Dotted lines indicate normals limits.

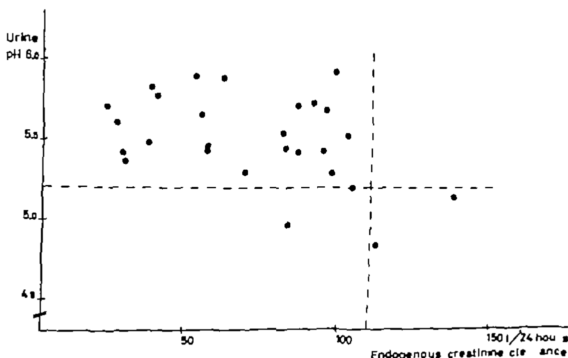


Fig. 20. Relationship of minimum urine pH to GFR in renal papillary necrosis. Each dot represents one individual. Dotted lines indicate normal limits.

Table VII

Renal papillary necrosis

Subject	Age	Sex	Before NH_4Cl: Endogenous creatinine clearance (l/d)	Before NH_4Cl: Total serum CO_2 (mEq/l)	Before NH_4Cl: Urine pH	Urine, 4—7 hours after NH_4Cl: Minimum pH	Urine, 4—7 hours after NH_4Cl: NH_4^+ (μEq/min)	Urine, 4—7 hours after NH_4Cl: Titratable acid (μEq/min)	Urine, 4—7 hours after NH_4Cl: Total CO_2 (μEq/min)	Urine, 4—7 hours after NH_4Cl: Urine flow (ml/min)
1	26	F	98	27.5	7.19	5.93	70	16	1.5	1.67
2.	62	F	57	27.5	6.32	5.43	35	18	1.5	1.08
3	43	F	81		5.67	5.54	41	20	1.3	2.08
4	56	F	62	25.5	6.61	5.89	52	10	1.2	2.00
5.	25	F	91	25.5	5.86	5.73	62	15	2.9	2.25
6	65	F	41	25	6.47	5.78	20	10	3.6	3.38
7	53	F	53	24.5	6.54	5.90	36	18	4.0	3.02
8.	54	M	67	26.5	6.10	4.99	34	30	1.2	1.47
9	56	F	112	25.5	5.70	4.84	51	23	1.5	1.92
10.	43	F	28	26	6.16	5.61	28	10	2.1	1.38
11	55	F	57	28	5.49	5.46	49	18	1.4	1.02
12	48	F	30	22.5	5.67	5.42	31	14	1.4	1.52
13.	43	F	94	25.5	6.33	5.43	20	15	1.2	1.32
14	48	F	84	24	7.19	5.72	19	21	3.1	1.59
15	57	F	137	30	5.49	5.14	48	26	3.8	4.19
16	60	F	83	24.5	5.27	4.97	52	26	2.6	2.39
17	27	F	69	23.5	5.69	5.30	38	20	2.2	2.60
18	43	F	104	25	5.64	5.20	61	33	2.8	2.25
19	30	F	84	22.5	5.83	5.42	28	20	2.2	2.16
20.	32	F	102	26	5.74	5.53	45	47	1.4	1.75
21.	32	F	25	17	5.88	5.71	18	14	1.3	1.71
22	31	F	82	26.5	6.48	5.45	34	21	2.8	2.38
23	53	F	38	27	5.60	5.48	30	14	2.6	3.20
24	28	F	94	21.5	6.33	5.69	23	16	1.2	2.17
25	40	F	31	22	5.77	5.37	22	31	1.8	2.16
26.	43	F	55	23.5	5.82	5.66	[illegible]	14	1.9	1.40
27	49	M	39	18.5	6.22	5.83	42	28	3.5	2.29
28	49	F	97	28	6.21	5.29	55	27	4.1	2.44
					Range:	4.84—5.93	18—70	10—47		

Table VI

Chronic non-obstructive pyelonephritis

Subject	Age	Sex	Before NH_4Cl: Endogenous creatinine clearance (l/d)	Before NH_4Cl: Total serum CO_2 (mEq/l)	Before NH_4Cl: Urine pH	Urine, 4—7 hours after NH_4Cl: Minimum pH	Urine, 4—7 hours after NH_4Cl: NH_4^+ (µEq/min)	Urine, 4—7 hours after NH_4Cl: Titratable acid (µEq/min)	Urine, 4—7 hours after NH_4Cl: Total CO_2 (µEq/min)	Urine, 4—7 hours after NH_4Cl: Urine flow (ml/min)
1	47	F	87	27.5	5.56	4.90	30	14	1.3	1.79
2.	51	F	80	27	5.92	5.19	38	18	3.3	2.33
3	26	F	56	25	7.09	5.04	32	23	1.1	1.18
4	58	F	75	28.5	5.37	5.01	37	19	1.5	1.07
5	39	F	119	24	5.36	5.04	45	31	2.4	2.17
6.	43	F	144	25.5	6.00	5.30	32	13	0.9	0.93
7	35	F	47	25	6.38	5.15	41	18	1.8	2.03
8	46	F	83	28.5	4.89	4.57	31	30	1.0	1.22
9	24	F	152	25	5.56	4.94	48	19	0.8	0.97
10	56	F	34	21.5	5.95	5.27	18	14	0.6	0.93
11	53	F	41	29	5.85	5.05	31	23	1.7	1.78
12.	34	F	42	22.5	5.39	4.99	14	23	1.9	2.13
13	55	F	87	23.5	5.36	4.39	52	37	1.1	3.00
14	61	F	92	27.5	5.93	4.91	37	28	3.4	3.29
15	52	F	63	24.5	5.64	5.29	31	19	2.0	1.70
16.	58	F	125	27	6.68	4.80	48	37	1.7	2.17
17	56	F	99	25.5	5.65	4.63	35	22	1.5	1.50
18	43	F	87	22.5	6.19	5.18	37	23	2.4	3.03
19	45	F	135	25	6.75	4.71	48	35	1.8	1.20
20.	57	F	26	21.5	5.72	5.38	34	12	1.0	1.80
					Range	4.39—5.38	14—52	12—37		
Range in 13 healthy subjects						4.65—5.05	26—78	19—55		
Range in the normal series of WRONG & DAVIES						4.60—5.24	33—75	24—51		

Table VII

Renal papillary necrosis

			Before NH_4Cl			Urine, 4–7 hours after NH_4Cl				
Subject	Age	Sex	Endogenous creatinine clearance (l/d)	Total serum CO_2 (mEq/l)	Urine pH	Minimum pH	NH_4^+ (μEq/min)	Titratable acid (μEq/min)	Total CO_2 (μEq/min)	Urine flow (ml/min)
1	26	F	98	27.5	7.19	5.93	70	16	1.5	1.67
2	62	F	57	27.5	6.32	5.43	35	18	1.5	1.08
3.	43	F	81		5.67	5.54	41	20	2.5	2.08
4	56	F	62	25.5	6.61	5.89	52	10	1.2	2.00
5	25	F	91	25.5	5.86	5.73	62	13	2.9	2.23
6	65	F	41	25	6.47	5.78	20	10	3.6	3.58
7	53	F	53	24.5	6.54	5.90	36	18	4.0	3.02
8	54	M	67	26.5	6.10	4.99	34	30	1.2	1.47
9	56	F	112	25.5	5.70	4.84	51	23	1.5	1.92
10.	45	F	28	26	6.16	5.61	28	10	2.1	1.38
11	55	F	57	28	5.49	5.46	49	18	1.4	1.02
12.	48	F	30	22.5	5.67	5.42	31	14	1.4	1.52
13	43	F	94	25.5	6.33	5.43	20	15	1.2	1.32
14	48	F	86	24	7.19	5.72	19	21	3.1	1.59
15	57	F	137	30	5.49	5.14	48	26	3.8	4.19
16	60	F	83	24.5	5.27	4.97	52	26	2.6	2.39
17	27	F	69	23.5	5.69	5.30	38	20	2.2	2.60
18	43	F	104	25	5.64	5.20	61	33	2.8	2.25
19	30	F	86	22.5	5.83	5.42	28	20	2.2	2.16
20	32	F	102	26	5.74	5.53	55	47	1.4	1.75
21.	32	F	25	17	5.88	5.71	18	14	1.3	1.71
22	31	F	82	26.5	6.48	5.45	34	21	2.8	2.38
23	53	F	38	27	5.60	5.48	30	14	2.6	3.20
24	28	F	95	21.5	6.33	5.69	23	16	1.2	2.17
25	40	F	31	22	5.77	5.37	22	31	1.8	2.16
26	43	F	55	23.5	5.82	5.66	26	14	1.9	1.40
27	49	M	39	18.5	6.22	5.83	42	28	3.5	2.29
28.	49	F	97	28	6.21	5.29	35	27	4.1	2.44
					Ranges:	4.84—5.93	18—70	10—47		

ammonium and urine pH is shown in fig 21 In both series of patients the excretion of ammonium was within normal limits (95 per cent range) for their urine pH with a few exceptions. There was, however a greater spread of values in the series of renal papillary necrosis and in some cases even a tendency towards larger amounts of ammonium than expected at their urine pH.

There was also a great spread in the values of titratable acid in both series (tables VI VII) Compared with the 13 normal subjects there was sometimes a slightly to moderately reduced excretion of titratable acid, but there was no certain difference between the two series of patients

The total serum CO_2 before the test is plotted against the minimum pH in fig. 22 At any level of total serum CO_2 the minimum pH was lower in the pyelonephritic than in the papillonecrotic group

The bicarbonate excretion was negligible in most cases (tables VI VII)

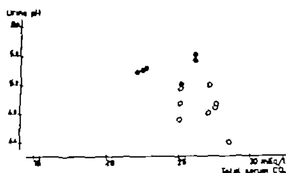


Fig 22. Correlation of minimum urine pH to the level of serum CO_2 in the clinical steady state.

o Chronic non-obstructive pyelonephritis.

● Renal papillary necrosis.

Discussion.

Like Wrong's & Davies's cases of general renal failure" our patients with pyelonephritis were able to produce a normal minimum pH in urine, whereas the cases of renal papillary necrosis were unable to accomplish this. The results are in accordance with the assumption that the final acidification of urine takes place in the collecting ducts, even in man Evidently the tubular epithelium in chronic pyelonephritis can maintain a normal hydrogen ion gradient even at an advanced renal impairment with low concentrating capacity The acidifying capacity in acute pyelonephritis seems also to be maintained, as indicated by Winberg's study in children (161)

The normal or slightly reduced excretion of ammonium in this material is not in agreement with the findings by Wrong & Davies. In their study cases with general renal impairment including chronic pyelonephritis had a considerably reduced excretion rate of ammonium. This is probably explained by the higher degree of renal impairment in their material (the mean creatinine clearance around 30 ml/min) Kleeman et al (71) also found a reduction of ammonium excretion in chronic pyelonephritis, and Fenel (31) found this reduction to be considerable when the maximum specific gravity was below 1 020

Briggs et al. (14) claim that the impaired excretion of ammonium is due to reduced intake of food, especially of protein and consequently reduced excretion of metabolic acids. Nephritic and non nephritic patients on the same acid ash regimen showed no difference in ammo-

nium excretion, whereas titratable acid was slightly higher and pH was lower in the nephritic urines.

Wrong & Davies found that the ammonium excretion was more closely related to the GFR than to the exact type of renal disease. Cases with potassium depletion or renal tubular acidosis, who could not produce a low urine pH, excreted *normal or elevated* amounts of ammonium for their urine pH. In the present series of renal papillary necrosis there were cases, which produced a relatively high amount of ammonium for their pH, in this respect resembling Wrong's & Davies's cases of specific tubular defects.

Potassium depletion, hypercalcemia and hydronephrosis as sources of error seem to have been excluded fairly well in the present study (see pages 46 and 49).

One fact to be borne in mind regarding this short test of acidifying capacity is that while the minimum pH is reached completely or practically completely the maximum excretion of ammonium and titratable acid is reached only in cases of chronic acidosis. In other cases the level of ammonium excretion depends on different degrees of enzyme adaptation. The fairly similar excretion rates of ammonium in chronic pyelonephritis and renal papillary necrosis suggest that no considerable ammonium excretion takes place in the collecting ducts. However according to the discussion above, no conclusions on this point can be drawn from the present values.

The normal subjects in the present investigations produced a urine pH ranging from 4.65 to 5.03 compared with 4.60 to 5.24 in the normal material of Wrong & Davies and 4.49 to 5.34 in the normal material of Pitts et al. (110). The regression line for the normal relationship between ammonium excretion and urine pH, as calculated by Wrong & Davies has been used. The healthy subjects in this study were distributed within the same normal range.

Cases with urea-splitting bacteria were to a great extent excluded from this study. However some cases with coliform bacteria are included. Some strains of coliform bacteria can exert a low degree of urea-splitting activity but this is apparent in vitro first after some days (28). Typing of coliform bacteria has not been performed. Thus, it is not known whether any of the cases recorded here had bacteria with above mentioned ability. In two cases with coliform bacteria, determinations of ammonium were made immediately after the urine was collected and the following day and identical results were obtained. None of the cases with coliform bacteria showed high values of ammonium excretion except two cases with high values of endogenous creatinine clearance.

In 23 patients the minimum pH was reached during the first period (4—5 hours after the acid load) and in 25 patients during the second period (6—7 hours after the load). The *urine flow for the corresponding period* varied between *0.9 and 3 ml/min.* in 42 patients and between 3 and *4.2 ml/min.* in 6 patients (*tables VI, VII*). The influence of a water diuresis on the hydrogen ion

excretion was investigated by Nutbourne & de Wardener (101) Nine normal subjects were submitted to ammonium chloride load for 5 or 6 days. The urine pH, titratable acid, ammonium and some other data were determined at a urine flow between 0 64 and 1 87 ml/min. and compared to the findings at a *flow between 10 5 and 18.2* ml/min. During the diuresis there was a rise in pH (0 4—1.2) and a fall in the excretion of [titratable acid -CO_2] but no significant change in ammonium excretion. We tested three normal subjects in a similar way during the short acidifying test. Two subjects, who increased their urine flow from 1.3 and 2 1 ml/min to 9.5 and 12.5 ml/min showed a rise in pH from 4.71 and 5 05 to 5 68 and 6.32 The third subject, who increased the diuresis from 0 6 to 6 ml/min. showed a rise in pH from 4 83 to 4 93 a change which slightly exceeds the error for measurement of pH. From these results it might be concluded that a considerable water diuresis is needed to give significant rise of urine pH. Therefore the variations in urine flow in the present investigation should be of no importance. However variations in urine flow might influence the urine pH more in the diseased kidney For that reason two cases of renal papillary necrosis were submitted to the above mentioned study For the present material it sufficed to show if a diuresis up to 4 ml/min. gave a rise in pH The two cases did not demonstrate any rise in pH. The fact that about half of the patients reached their minimum pH during the first period and the other half during the second period is not explained by any reverse relationship to the urine flow The differences in urine flow between the two periods exceeded 1 ml/min in only eight cases.

When comparing concentrating and acidifying capacity in the series of renal papillary necrosis, it is evident that the concentrating capacity is the most sensitive indicator of renal damage in early cases of this disorder

Renal function data in two cases — one from each series — are given in the legends of figs. 2 and 3

Summary

Renal papillary necrosis with a slowly progressive course has been frequently diagnosed during later years. In the literature there is strong evidence suggesting a causal relation between prolonged consumption of phenacetin and renal papillary necrosis. It has also been claimed that this kind of renal damage could develop in the absence of urinary tract infection.

One purpose of this study was to analyse the interrelationship of infection and prolonged use of phenacetin in chronic non-obstructive pyelonephritis and in renal papillary necrosis.

A further purpose was to compare the incidence of hypertension and some functional patterns in the two series.

A clinical material of 169 patients was included in the study: 75 cases of chronic non-obstructive pyelonephritis and 94 cases of renal papillary necrosis. A rigorous selection had been made in order to exclude obstructive uropathies and other kinds of urinary tract lesions. Patients with diabetes mellitus were also excluded. For women an upper age limit was set at 65 years, since micturition disturbances are common in higher ages. For men an upper age limit was set at 55 years in order to avoid cases with occult prostatic diseases.

The female preponderance was overwhelming, only 11 males being included in the material, and all of them belonged to the series of renal papillary necrosis. The mean age was 47 years and the age distribution was the same in both series.

The diagnosis of chronic pyelonephritis was based on clinical and roentgenologic criteria, and 15 cases were also examined histopathologically. In 6 of these case the clinical criteria alone had not been enough for the diagnosis. The diagnosis of renal papillary necrosis was based on histopathologic examination in 30 cases and solely on roentgenologic examination in 64 cases.

There was agreement between roentgenologic and histopathologic findings in all of 12 patients with chronic pyelonephritis and in all of 22 patients with renal papillary necrosis, in whom the renal impairment was not to advanced to obtain a judgeable intravenous urography.

Results and conclusions

1. A history of acute pyelonephritis was common, being present in about 70 per cent in both series. There was no pre-

excretion was investigated by Nutbourne & de Wardener (101) Nine normal subjects were submitted to ammonium chloride load for 5 or 6 days. The urine pH titratable acid, ammonium and some other data were determined at a urine flow between 0 64 and 1 87 ml/min and compared to the findings at a flow between 10.5 and 18.2 ml/min. During the diuresis there was a rise in pH (0 4—1 2) and a fall in the excretion of [titratable acid -CO_2] but no significant change in ammonium excretion We tested three normal subjects in a similar way during the short acidifying test. Two subjects, who increased their urine flow from 1.3 and 2 1 ml/min. to 9 5 and 12.5 ml/min. showed a rise in pH from 4.71 and 5 05 to 5 68 and 6.32. The third subject, who increased the diuresis from 0 6 to 6 ml/min. showed a rise in pH from 4 83 to 4 93 a change which slightly exceeds the error for measurement of pH. From these results it might be concluded that a considerable water diuresis is needed to give significant rise of urine pH. Therefore the variations in urine flow in the present investigation should be of no importance. However variations in urine flow might influence the urine pH more in the diseased kidney For that reason two cases of renal papillary necrosis were submitted to the above mentioned study For the present material it sufficed to show if a diuresis up to 4 ml/min gave a rise in pH. The two cases did not demonstrate any rise in pH. The fact that about half of the patients reached their minimum pH during the first period and the other half during the second period is not explained by any reverse relationship to the urine flow The differences in urine flow between the two periods exceeded 1 ml/min. in only eight cases

When comparing concentrating and acidifying capacity in the series of renal papillary necrosis, it is evident that the concentrating capacity is the most sensitive indicator of renal damage in early cases of this disorder

Renal function data in two cases — one from each series — are given in the legends of figs. 2 and 3

4 The concentrating capacity was estimated by the pitressin tannate test. The maximal urine osmolality was then correlated to the endogenous creatinine clearance, which was used as a clinical measure of GFR. Disorders known or suspected to affect these renal functions were excluded besides temporary obstructions and hydronephrosis, potassium depletion and hypercalcemia were excluded as well as acute exacerbations of the pyelonephritis.

There was a proportionate reduction of the concentrating capacity and the GFR in the series of chronic non-obstructive pyelonephritis. In the series of renal papillary necrosis the concentrating capacity was reduced relatively more than the GFR. In this respect the difference between the two series was highly significant. With increasing renal impairment the regression lines converged and intersected below an endogenous creatinine clearance of 20 1/24 hours.

A control series of essential hypertension was studied in the same way. In this series the GFR was reduced at an earlier stage than the concentrating capacity.

5 The renal acidifying capacity was estimated by a short test of ammonium chloride loading, which gives the minimum pH but not the maximum excretion rate of ammonium and titratable acid. The clinical criteria used were the same as for the concentrating test.

The patients with chronic non-obstructive pyelonephritis maintained the ability to excrete an acid urine even at an advanced reduction of the GFR. Most of the patients with renal papillary necrosis were unable to excrete urine of normal minimum pH even at a slight or moderate reduction of the GFR. The difference beteen the two series was highly significant.

The relationship between excretion of ammonium and urine pH was within normal limits (95 per cent range) in both series. In the series of renal papillary necrosis there was even a tendency towards larger amounts of ammonium than expected at their urine pH. Cases with usually urea-splitting bacteria such as *Proteus* and *Staphylococcus* had been excluded. There was a great spread in the values of titratable acid but no difference between the two series.

When comparing concentrating and acidifying capacity it is evident, that the concentrating capacity is the most sensitive indicator of renal damage in early cases of renal papillary necrosis.

The demonstrated difference in function pattern between renal papillary necrosis and chronic non-obstructive pyelonephritis without papillary necrosis can be used in the differential diagnostics of these two variants of renal disease.

ponderance of cases with an *insidious* course in the groups with advanced renal damage. The strikingly similar frequency of acute pyelonephritis and of other urinary tract infections in the two series provides strong evidence that renal papillary necrosis *is a morphologic* variant of chronic pyelonephritis.

2. Chronic phenacetin consumption was common in both series. The *incidence* was, however, more than *twice as* high in the series of renal papillary *necrosis* (79 per cent) *as in the* series of chronic non-obstructive pyelonephritis (36 per cent). If only patients with a consumption of at least 1 g phenacetin daily were counted, the figures were 60 per cent and 23 per cent respectively. The duration of the consumption had also been longer in the series of renal papillary *necrosis*. The difference in time factor was especially striking, when the start of phenacetin consumption was related to the date of first noted signs of infection. In no less than 43 per cent of the series of papillary necrosis did the start of the phenacetin consumption precede the signs of infection by more than 10 years. This suggests that phenacetin has often been the primary factor in renal damage. However, it is not indicated that phenacetin was the only factor for development of renal damage. Thus, chronic phenacetin consumption was combined with a history of acute pyelonephritis in 78 per cent in the series of chronic pyelonephritis and in 68 per cent in the series of papillary necrosis. Whether phenacetin or bacteria are supposed to be the primary factor for the renal damage, the conclusion will be that *once* the kidney is diseased, prolonged use of phenacetin frequently causes *papillary* necrosis.

The *eleven males in the* series of papillary necrosis were all consumers of phenacetin. This fact and the absence of males in the series of chronic *non-obstructive* pyelonephritis lead to the conclusion *that chronic* pyelonephritis in males (with or without papillary necrosis) *is rare or non-existent*, unless there is some predisposing factor — diabetes mellitus, primary uropathy or chronic phenacetin consumption.

3. The incidence of hypertension and the mean diastolic blood pressure was higher in the series of chronic *non-obstructive* pyelonephritis than in renal papillary necrosis. When each series was subdivided into three function groups there was a clear trend of increasing blood pressure with increasing renal impairment in both series (mean diastolic pressure 95 → 102 → 112 mm Hg in the first series and 86 → 95 → 102 mm Hg in the second series). The age distribution was the same within the three function groups of both series. In the second series no case with a serum creatinine level below 2.5 mg% showed a diastolic blood pressure above 110 mm Hg, unless there was a positive family history of hypertension. The frequency of a positive family history of hypertension was the same in both series.

It was concluded that renal papillary necrosis *per se* might have some blood pressure reducing effect. The possible mechanism for this effect was discussed.

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ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 387

THE DIAGNOSTIC VALUE OF UNIPOLAR PRECORDIAL PATTERNS OF VENTRICULAR PREMATURE BEATS IN MYOCARDIAL INFARCTION

BY

V.-M. ANTTONEN, EILA LESKINEN
LAURI MEURMAN, MARTTI OKA
and HERTTA RAUNIO

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From the Department of Medicine (Head, V. M. Anttonen, M. D.)
and
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INTRODUCTION

Myocardial infarction does not always produce electrocardiographic changes in the sinus beats which could be used to confirm the diagnosis. In these cases, changes occurring in the ventricular premature beats (VPB) may be diagnostically significant (Dressler 1943, Simonsen, Enzer & Goldman 1945 Somerville & Wood 1949 Katz, Berk & Mayman 1958 Soffer 1959)

The great importance of VPB in the diagnosis of myocardial infarction has been demonstrated by Anttonen, Oka and Holopainen (1959) In a series of 502 hospitalized patients with acute myocardial infarction, repeated electrocardiographic tracings showed VPB in 47 cases. The patterns of infarction were evident in the VPB in 39 cases. In 27 cases the infarction patterns were present simultaneously in the normal rhythm and the VPB. In 12 cases the infarction patterns appeared earlier or more distinctly in the VPB than in the normal rhythm or the infarction patterns occurred in the VPB only

In the afore-mentioned paper when discussing these findings the following statements were made An electrical field between injured and intact tissue precipitates extrasystoles. The left ventricle is injured by myocardial infarction more often than the right. Thus the VPB occurring in connection with myocardial infarction usually originate in the left ventricle, e.g. the tracings may show QRS complexes similar to those seen in right bundle branch block. This is very fortunate because the electrocardiographic changes of myocardial infarction can be more easily recognized in right bundle branch block than in left. For instance a septal infarction with right bundle branch block can be diagnosed easily from the characteristic QRS complexes in right unipolar chest leads

Thus we concluded that a qR (*QR*) pattern of a left VPB has the same diagnostic value as that of right bundle branch block, e.g. it is in most instances a sign of infarction of the interventricular septum. Further the presence of a septal Q wave (qR or QR complex) of a left VPB in the right precordial leads was in our opinion the most pathognomonic infarction pattern of the VPB. It was emphasized, however that in subjects with enlargement of the right atrium and right ventricle the qR pattern of a left VPB *may be present* in Leads V and V even in the absence of septal infarction.

Our findings indicated also that the presence of the QS pattern of VPB in Leads V_2 and V was a very suggestive

sign of infarction of the interventricular septum especially when it appeared in these precordial leads only

Our clinical observations were confirmed by Soloff (1961) and Bisteni, Medrano and Sodi-Pallares (1961) The latter were able to show in their experimental studies with dogs that the unipolar patterns of VPB diagnostic of septal infarction were indeed of the QR type (QR, QRs or Qrs complexes)

However results obtained by experiments with animals cannot be applied without reservation in clinical medicine since the heart muscle and coronary arteries of the experimental animals are intact before the provoked infarction, what is rather exceptional in patients with myocardial infarction.

The purpose of the present investigation has been to expand and deepen our knowledge of the diagnostic value of the unipolar precordial patterns of VPB by clinical and post mortem studies the latter having been described hitherto in only three cases of myocardial infarction (Bisteni Medrano & Sodi Pallares)

MATERIAL AND METHODS

A total of 27,391 electrocardiograms of 17,056 hospitalized patients were examined for the presence of VPB in the precordial leads. The forms of the VPB were examined for the presence of QR complexes, and the origins of the VPB were also determined when possible.

The history and clinical, roentgenological and laboratory findings as well as the electrocardiographic changes in the dominant rhythm of the cases with VPB were reviewed.

The diagnosis of myocardial infarction was made on the basis of history clinical symptoms, electrocardiographic changes in sinus (dominant) beats, serum glutamic oxalacetic transaminase and or C-reactive protein estimations, at least three out of four or four out of five criteria being positive.

The diagnosis »coronary artery disease« was made in cases with a history of angina pectoris and electrocardiographic signs of coronary insufficiency.

The cases without heart disease» presented no anamnestic, clinical, roentgenological or electrocardiographic evidence of heart disease.

The cases with VPB of the QR type in the precordial leads are presented in Table 1. The relationship between the presence of VPB of the QR type and the electrical site of the myocardial infarction (determined by changes in the dominant rhythm) is presented in Table 2.

Post-mortem studies were performed in 18 cases with VPB of the QR type (Cases 1—18). The relationship between the site of infarction and the presence of the QR pattern of VPB in the 17 autopsied cases with myocardial infarction is shown in Table 3.

Attention was also drawn in cases with myocardial infarction to the presence of VPB resembling left bundle branch block but with the special characteristic of having a prominent R wave in right precordial leads. We have regarded these as right VPB (Cases 8 19 20, 21).

Finally VPB produced mechanically and recorded in precordial leads during cardiac catheterization were examined. Two illustrative cases are described (Cases 22 and 23).

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Finally VPB produced mechanically and recorded in precordial leads during cardiac catheterization were examined. Two illustrative cases are described (Cases 22 and 23)

RESULTS

(1) *The presence of VPB of the QR type in non-autopsied cases*

Of the 575 cases in which VPB were found, 126 had the QR *pattern in VPB* (Table 1) In only one case was this pattern present in an otherwise normal heart. The remaining 125 cases had symptoms of heart disease. The exceptional *subject was a 23-year-old female* with pneumonia and a history of diphtheria and joint involvement.

Of the 125 subjects with myocardial infarction and VPB 78 (62 per cent) presented the QR pattern in the VPB 58 of the VPB of the QR type probably originated in the left ventricle and 7 in the right. In 13 instances it was impossible to define the origin of the VPB In the presence of myocardial infarction and VPB of defined origin the QR pattern occurred in most instances in the leads, which reflected the potential variations of the epicardial surface of the ventricle contralateral to the site of origin e.g. in the right precordial leads in the presence of a left VPB and in the left precordial leads in the presence of a right VPB Eight cases with evidence of extensive myocardial infarction however had the QR pattern in the VPB in all precordial leads. Of these five *had left VPB and three* VPB of undefined origin.

Of the 243 cases with coronary artery disease and VPB 34 (14 per cent) had *VPB of the QR type. All* 34 had distinct electrocardiographic signs of coronary insufficiency (RS-T displacements and T wave abnormalities) in the dominant rhythm. Among these patients may be subjects with undiagnosed myocardial infarction, for it has *to be borne in mind that our diagnostic* criteria were very strict. 125 cases in the group coronary artery disease had simultaneous signs of congestive heart failure (in most instances left heart failure) The presence of congestive heart failure in subjects with coronary artery disease did not seem to lead to any significant increase in the incidence of the QR pattern in VPB. Of the 118 cases with coronary artery disease without congestive heart failure 15 (13 per cent) had the QR pattern in VPB while 19 cases (15 per cent) of the 125 cases with combined coronary artery disease and congestive heart failure presented the same pattern. It can be suggested that in cases with coronary artery disease the presence of VPB of the QR type is in most instances a sequel of undiagnosed myocardial infarction.

Table 1 shows that VPB of the QR type occurred quite frequently in subjects with cor pulmonale and mitral or

Table 1 Occurrence of ventricular premature beats of the QR type in various heart diseases and in cases without heart disease

Clinical diagnosis	No. of cases with VPB	VPB of QR type (No. of cases)												Total
		Right precordial leads			Leads V and V			Left precordial leads			Leads V to V			
		Left VPB	Right VPB	Undefined VPB	Left VPB	Right VPB	Undefined VPB	Left VPB	Right VPB	Undefined VPB	Left VPB	Right VPB	Undefined VPB	
Myocardial infarction	123	53	0	6	0	0	1	0	7	3	5	0	3	78
Coronary artery disease	243	27	0	3	0	0	4	0	0	0	0	0	0	34
Cor pulmonale	30	2	0	1	0	0	0	0	0	0	0	0	0	3
Mitral valvular disease	19	3	0	1	0	0	0	0	0	0	0	0	0	4
Aortic valvular disease	25	3	0	2	0	0	0	0	0	0	0	0	0	5
Congenital heart disease	3	0	0	0	0	0	0	0	0	0	0	0	0	0
Myocardiopathy	18	1	0	0	0	0	0	0	0	0	0	0	0	1
Subjects without heart disease	122	0	0	0	0	0	1	0	0	0	0	0	0	1
Total	573	89	0	13	0	0	6	0	7	3	5	0	3	126

aortic valvular disease It has to be mentioned that it was impossible to define the origin of the VPB in many cases. All three cases with cor pulmonale and VPB of the QR type had distinct signs of right heart enlargement and failure. The same was the case in the four subjects with mitral valvular disease and with early negativity of the QRS complexes in the VPB However in the subjects with mitral valvular disease and VPB the initial Q wave was not very prominent in most instances, showing a qR complex instead of the QR complex. It was further found that all the cases with aortic valvular disease and VPB of the QR type presented signs of enlargement of the whole heart (and left and right heart failure)

It is possible that among the subjects with cor pulmonale and mitral and aortic valvular disease there may also be some hidden cases of myocardial infarction, even though the anamnestic, clinical laboratory and electrocardiographic signs were absent. At all events, the results of this study support the concept described earlier by us (Anttonen, Oka & Holopainen) that left VPB of the qR (QR) type may occur in the presence of right heart enlargement without myocardial infarction

A case with myocardiopathy and left VPB of the QR type had electrocardiographic signs of myocardial ischemia in the sinus beats (distinctly negative T wave in Leads V_1 through V_4) However other evidence of coronary artery disease or myocardial infarction was lacking.

It has to be stressed again that of the 122 subjects without heart disease only one had VPB of the QR type

(2) *The presence of VPB of the QR type in cases with electrocardiographic evidence of myocardial infarction.*

Of the 67 patients with electrocardiographic signs of infarction of the interventricular septum in the sinus beats, 58 (87 per cent) had VPB of the QR type. Of the 58 cases without evidence of septal infarction in the sinus beats, 20 (35 per cent) had VPB of the QR type (Table 2)

Table 2. The relationship between the electrical site of myocardial infarction and the occurrence of the QR pattern in ventricular premature beats

Electrical site of infarction	*No. of cases with VPB*	*No. of cases with VPB of QR type*
Anterior	7	3
Anteroseptal	46	40
Anterolateral	19	3
Anteroseptallateral	20	17
Inferior	11	4
Inferoseptal	1	1
Inferolateral	20	9
Strictly posterior	1	1
Total	125	78

Determined by QRS changes and T wave abnormalities in the sinus beats.

In our previous study we took the view that the presence of VPB of the QR type may reveal septal involvement in subjects with anterior and/or posterior myocardial infarction even though no electrocardiographic signs of septal infarction are present in the

Table 3. The relationship between the site of myocardial infarction and the occurrence of the QR pattern in ventricular premature beats in 17 autopsied cases.

Site of infarction	*VPB of QR type (No. of cases)*								
	Right precordial leads			*Leads V to V_4*			*Left precordial leads*		
	Left VPB	*Right VPB*	*Undetermined VPB*	*Left VPB*	*Right VPB*	*Undetermined VPB*	*Left VPB*	*Right VPB*	*Undetermined VPB*
Anteroseptal	2	0	0	0	0	0	0	2	1
Anteroseptalposterior	6	0	0	1	0	0	1	1	0
Posteroseptal	1	0	0	0	0	0	0	0	0
Posterolateral	2	0	0	0	0	0	0	0	0
Total	11	0	0	1	0	0	1	3	1

sinus beats. These observations have been confirmed by Bisteni, Medrano and Sodi-Pallares. Our present study also supports this view

(3) *The presence of VPB of the QR type in autopsied cases.*

Of the 18 cases with VPB of the QR type and necropsy data available 17 had myocardial infarction (Cases 1—17) In 15 cases the infarction extended to the septum. In 2 cases only were signs of infarction of the interventricular septum absent (Cases 16 and 17) Both the patients had suffered from mitral valvular disease and congestive heart failure. There were also signs of infarction of the posterior wall of the left ventricle in both cases.

Of the 17 cases with myocardial infarction and VPB of the QR type, 13 had a left VPB and 3 a right (Table 3) The origin of the VPB could not be determined in one case. Of the 13 cases with a left VPB, 11 had the QR pattern in the right precordial leads and one in the left. In one subject with a left VPB of the QR type, the QR pattern was present in Leads V through V_6. All 3 cases with a right VPB of the QR type presented it in the left precordial leads. In the subject with VPB of the QR type of undetermined origin, the QR pattern was present in the left precordial leads.

Of the 15 cases with septal infarction and VPB of the QR type, 8 only showed distinct electrocardiographic evidence of infarction of the inter ventricular septum in the dominant rhythm. In 7 instances (Cases 1, 4, 7 12, 13, 14, 15) the septal infarction was disclosed by the QR patterns of the VPB alone.

It must be emphasized that a left VPB of the QR type occurred only once in the absence of myocardial infarction (Case 18) This was a case with chronic cor pulmonale and distinct enlargement of the right ventricle.

Thus the post mortem findings were consistent with our previous and present clinical observations, which indicate *that the presence of VPB of the* QR type is a very important sign of infarction of the interventricular sept um in subjects without heart dilatation.

(4) *The presence of right VPB with a prominent initial R wave (RS complex) in the right precordial leads in cases with myocardial infarction.*

Of the 7 cases with electrocardiographic evidence of myocardial infarction and a right VPB of the QR type in the left precordial leads (Table 1) 2 simultaneously had a prominent initial R wave in *Lead* V_1 *diminishing in size* from right to left across most of the precordium. Both cases had electrocardiographic signs of an extensive anterior myocardial infarction (*see* Fig 19)

We have further found a prominent initial R wave in the right VPB in Lead V_1 in 3 cases with myocardial infarction involving the septum (Cases 9 20 and 21) *It should be noted that* only once was the QR pattern of right VPB simultaneously present in the left precordial leads (Case 9)

(5) *The unipolar precordial patterns of VPB produced by cardiac catheterization in children with atrial septal defect.*

In two children with atrial septal defect catheterization of the left ventricle *produced left VPB of the QR type* in the right precordial leads (Cases 22 and 23)

We have further found that right VPB produced by catheter may show deflection with a prominent initial positivity in the right precordial leads in *cases with atrial septal defect in the* absence of myocardial infarction (Case 23)

DISCUSSION

It is generally accepted that the morphology of VPB cannot be used to diagnose the underlying heart disease, because in many instances the origin of the VPB cannot be determined with any certainty and the spread of the excitation is frequently uneven and bizarre. Th exact determination of the origin of the VPB is difficult or even impossible by electrocardiography especially in the presence of ventricular hypertrophy and myocardial infarction. Vectorcardiography can be useful in these cases (Wegnar Engelhart & Mäsalacher 1959)

It is obvious that the origin of VPB cannot be defined if it is simultaneously present in a few tracings only The tracings were recorded in the present study with 2- 3- or 4-channel electrocardiographs.

However there are numerous VPB in which the origin can be determined from their electrocardiographic patterns. It has been found that when VPB arise in the free walls of both ventricles or in the septal mass, the ventricular activation is usually similar to that of right and left bundle branch block.

Consequently the forms of VPB originating in the free wall of the left ventricle or in the left *septal mass* resemble the form of complete right bundle branch block, and the forms of VPB arising in the free wall of the right ventricle or right septal mass resemble the form of complete left bundle branch block. However this is the case only when the activation of the whole heart depends on the ectopic stimulus and the possibility of a fusion beat» has been excluded (Bisteni, Sodi-Pallares, Medrano & Pileggi 1960)

VPB originating in the upper and posterior portions of the interventricular septum may also have a morph ology resembling bundle branch block, but with a special characteristic of positive QRS complexes in all precordial leads.

The diagnosis of myocardial infarc tion from the unipolar precordial patterns of VPB can be made in the cases in which the forms of the VPB *resemble those of right and left bundle* branch block. In other cases difficulties frequently arise in the definition of the origin of VPB and diagnosis of infarction.

However to be able to diagnose myocardial infarction by the unipolar pat terns of VPB, one has to interpret these in the same way as similar patterns in the presence of bundle branch block (Anttonen, Oka & Holopainen, Bisteni, *Medrano & Sodi-Pallares)*

It is well known that in the presence

Thus the post-mortem findings were consistent with our previous and present clinical observations, which indicate that the presence of VPB of the QR type is a very important sign of infarction of the interventricular septum in subjects without heart dilatation.

(4) The presence of right VPB with a prominent initial R wave (RS complex) in the right precordial leads in cases with myocardial infarction.

Of the 7 cases with electrocardiographic evidence of myocardial infarction and a right VPB of the QR type in the left precordial leads (Table 1) 2 simultaneously had a prominent initial R wave in Lead V_1 diminishing in size *from right to left across most of the* precordium. Both cases had electrocardiographic signs of an extensive anterior myocardial infarction (see Fig. 19)

We have further found a prominent initial R wave in the right VPB in Lead V_1 in 3 cases with myocardial infarction involving the septum (Cases 9 20 and 21) It should be noted that only once was the QR pattern of right VPB simultaneously present in the left precordial leads (Case 9)

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We have further found that right VPB produced by catheter may show deflection with a prominent initial positivity in the right precordial leads in cases with atrial septal defect in the absence of myocardial infarction (Case 23)

diagnostic significance of this electrocardiographic pattern has not been previously pointed out in connection with VPB. Therefore it is necessary to discuss the factors which influence the occurrence of deflections with prominent initial positivity (the RS complex) in the right precordial leads.

In the presence of a right VPB (and left bundle branch block) the early forces of activation of the apex of the *right ventricle* are presumably neutralized by the larger right-to-left activation of the septum and thus QS or rS deflections are found in Leads V_1 and V_2. In the presence of infarction of the interventricular septum and a right VPB, the vectors representing the *early forces of right ventricular activation* may be directed to the right and anteriorly producing a prominent R wave in the right precordial leads. These early QRS vectors may be relatively perpendicular to V_1 and V axes and projected on the negative field f the V and V axes. The following QRS vectors are probably deflected abruptly posteriorly Thus the infarction of the interventricular septum can be fol lowed by the appearance of a prominent R wave in the right precordial leads, of a rS or QS complex in Leads V and V and sometimes simultaneously of the QR complex in the left precordial leads in the right VPB (Case 19)

In the presence of right ventricular hypertrophy and right VPB increases in the voltage of the electrical vectors representing the activation of the free wall of the right ventricle probably result in the occurrence of a prominent R wave (RS complex) in the right precordial leads, even though signs of septal infarction are absent (Case 23)

It should also be mentioned that if the VPB arise in the posterior portions of the right ventricle the R wave may be prominent in Leads V and V even though septal infarction and right vent ricular hypertrophy are absent. Here, however the size of the R wave increases probably from right to left across the precordium. At all events, it can be concluded that the presence of the RS pattern in a right VPB in Leads V and V_2 is only a supportive sign of anteroseptal infarction.

Finally it has to be borne in mind that tracings obtained with an exploring electrode near the site of origin of VPB may show QS deflections or those *with embryonal initial positivity* even in the absence of myocardial infarction.

Our findings suggest, however that the QS pattern of VPB recorded in Leads V and V denotes the infarction of the interventricular septum even in cases in which the VPB arise in *other areas than the septum.* These investigations, as well as investigations on the diagnostic value of the patterns of VPB in the limb leads, will be the subject of future studies.

of right bundle branch block the QR pattern in the right precordial leads denotes an anteroseptal infarction and a similar pattern in the left precordial leads is a characteristic sign of involvement of the free wall of the left vent ricle However in subjects with right atrial enlargement a qR complex may be present in the right precordial leads even in the absence of myocardial infarction. This is the case both in normal ventricular activation and right bundle branch block and left VPB

It is generally agreed that in the presence of left bundle branch block the electrocardiogram seldom shows signs pathognomonic of myocardial infarction. In the presence of left bundle branch block and septal infarction, however the QR pattern may occur in the left precordial leads. The infarction of the interventricular septum can also not infrequently be recognized in left bundle branch block by the presence of a prominent R wave (RS complex) in Leads V_1 and V_2 diminishing in size from right to left across most of the precordium (Massie & Walsh 1960 Rhoads, Edwards & Pruitt 1961)

Our present clinical and post mortem findings indicate that the afore-mentioned unipolar electrocardiographic patterns really have the same diagnostic value in the presence of VPB and bundle branch block. Consequently the QR patterns of a left VPB in the right precordial leads and the QR patterns of a right VPB in the left precordial leads denote myocardial infarction with septal involvement. Further the presence of left VPB of the QR type in both right and left precordial leads is diagnostic of extensive anteroseptal infarction.

The necropsy data and observations in cardiac catheterization suggest however that the presence of the QR pattern in left VPB has only limited value in the diagnosis of myocardial infarction in cases with great dilatation of the heart, especially of the right atrium and/or ventricle. The diagnostic value of the QR pattern is also limited in fusion beats, where it may be present, even in the absence of myocardial infarction.

The post mortem findings further confirm our previous view that the presence of the unipolar patterns of VPB may in many cases be the only electrocardiographic sign of infarction of the interventricular septum. According to Bisteni Medrano and Sodi Pallares, in the presence of infarction of the lower third of the left septal mass, the infarction can be recognized only in the presence of asynchronous ventricular activation (as, for instance in left bundle branch block and in right VPB) since the forces generated by the lower third of the left septal mass are not easily identified during normal activation, because of the electrical predominance of the forces of the free left ventricular wall.

We have also found that the presence of a prominent initial R wave (RS complex) in right VPB in the right precordial leads (the R wave diminishing in size from right to left across the precordium) may have diagnostic value in myocardial infarction with septal involvement. So far as we know the

diagnostic significance of this electrocardiographic pattern has not been previously pointed out in connection with VPB. *Therefore it is necessary* to discuss the factors which influence the occurrence of deflections with prominent initial positivity (the RS complex) in the right precordial leads.

In the presence of a right VPB (and left bundle branch block) the early forces of activation of the apex of the right ventricle are presumably neutralized by the larger right-to-left activation of the septum and thus QS or rS deflections are found in Leads V and V_2. In the presence of infarction of the interventricular septum and a right VPB, the vectors representing the early forces of right ventricular activation may be directed to the right and anteriorly producing a prominent R wave in the right precordial leads. These early QRS vectors may be relatively perpendicular to V and V axes and projected on the negative field of the V and V axes. The following QRS vectors are probably deflected abruptly posteriorly. Thus the infarction of the interventricular septum can be followed by the appearance of a prominent R wave in the right precordial leads, of a rS or QS complex in Leads V and V and sometimes simultaneously of the QR complex in the left precordial leads in the right VPB (Case 19)

In the presence of right ventricular hypertrophy and right VPB, increases in the voltage of the electrical vectors representing the activation of the free wall of the right ventricle probably result in the occurrence of a prominent R wave (RS complex) in the right precordial leads, even though signs of septal infarction are absent (Case 23)

It should also be mentioned that if the VPB arise in the posterior portions of the right ventricle the R wave may be prominent in Leads V and V even though septal infarction and right ventricular hypertrophy are absent. *Here*, however the size of the R wave increases probably from right to left across the precordium. At all events, it can be concluded that the presence of the *RS* pattern in a right *VPB* in Leads V and V is only a supportive sign of anteroseptal infarction.

Finally it has to be borne in mind that tracings obtained with an exploring electrode near the site of origin of VPB may show QS deflections or those with embryonal initial *positivity even* in the absence of myocardial infarction.

Our findings suggest, however that the QS pattern of VPB recorded in Leads V and V denotes the infarction of the *interventricular septum* even in cases in which the VPB arise in other areas than the septum. These investigations, as well as investigations on the diagnostic value of the patterns of VPB in the *limb leads*, will be the subject of future studies.

of right bundle branch block the QR pattern in the right precordial leads denotes an anteroseptal infarction and a similar pattern in the *left* precordial leads is a characteristic sign of involvement of the free wall of the left ventricle However in subjects with right atrial enlargement a qR *complex* may be present in the right precordial leads even in the absence of myocardial infarction. This is the case both in *normal* ventricular activation and right bundle branch block and left VPB

It is generally agreed that in the presence of left bundle branch block the electrocardiogram seldom shows signs pathognomonic of myocardial infarction. In the presence of left bundle branch block and septal infarction however the QR pattern may occur in the left precordial leads. The infarction of the interventricular septum can also not infrequently be recognized in left bundle branch block by the presence of a prominent R wave (RS complex) in Leads V_1 and V_2 diminishing in size from right to left across most of the precordium (Massie & Walsh 1960 *Rhoads, Edwards & Pruitt 1961*)

Our present clinical and post mortem findings indicate that the afore-mentioned unipolar electrocardiographic patterns really have the same diagnostic value in the presence of VPB and bundle branch block. Consequently the QR patterns of a left VPB in the right precordial leads and the QR patterns of a right VPB in the left precordial leads denote myocardial infarction with septal involvement. Further the presence of left VPB of the QR type in both right and left precordial leads is diagnostic of extensive anteroseptal infarction.

The necropsy data and observations in cardiac catheterization suggest however that the presence of the QR pattern in left VPB has only limited value in the diagnosis of myocardial infarction in cases with great dilatation of the heart, especially of the right atrium and/or ventricle. The diagnostic value of the QR pattern is also limited in fusion beats, where it may be present, even in the absence of myocardial infarction.

The post mortem findings further confirm our previous view that the presence of the unipolar patterns of VPB may in many cases be the only electrocardiographic sign of infarction of the interventricular septum. According to Bisteni, Medrano and Sodi-Pallares, in the presence of infarction of the lower third of the left septal mass, the infarction can be recognized only in the presence of asynchronous ventricular activation (as, for instance in left bundle branch block and in right VPB) since the forces generated by the lower third of the left septal mass are not easily identified during normal activation, because of the electrical predominance of the forces of the free left ventricular wall.

We have also found that the presence of a prominent initial R wave (RS complex) in right VPB in the right precordial leads (the R wave diminishing in size from right to left across the precordium) may have diagnostic value in myocardial infarction with septal involvement. So far as we know the

also be produced by mechanical stimulation of the endocardium during cardiac catheterization in cases of atrial septal defect.

The following conclusions are drawn. (1) The QR patterns of ventricular premature beats in unipolar precordial leads have the same diagnostic significance as similar patterns in bundle branch block.

(2) The presence of the QR pattern of left ventricular premature beats in Leads V and V has only limited value in the diagnosis of myocardial infarction in cases with great dilatation of the heart.

3) The presence of a prominent initial R wave (RS complex) in right ventricular premature beats in Leads V_1 and V_2 (the R wave diminishing in size from right to left across the precordium) is a supportive sign of septal infarction.

(4) In many instances infarction of the interventricular septum can be diagnosed solely by the unipolar precordial patterns of ventricular premature beats.

SUMMARY AND CONCLUSIONS

The diagnostic significance of the unipolar precordial patterns of ventricular premature beats was studied *in a series of 27,391* electrocardiograms *of* 17 056 patients. Ventricular premature beats occurred in 575 cases, of which 126 presented ventricular premature beats of the QR type. Ventricular premature beats of the QR type *were* found in a normal heart *in only one case* in all the others there was heart disease.

The material included 125 cases of myocardial infarction with ventricular premature beats in the electrocardiogram. A QR pattern in ventricular premature beats was found in 62 per cent of these cases. In 58 *cases the* origin of the ventricular premature *beats* was in the *left* ventricle in 7 cases in the right and in 13 cases un defined.

Of the 67 cases with electrocardiographic signs of infarction of the inter ventricular septum in the sinus beats, 87 per cent showed ventricular premature beats of the QR type. Of the 58 cases without signs of septal infarction *in the sinus beats*, 35 per cent had ventricular premature beats of the QR type

Of the 243 cases with coronary artery disease and ventricular premature beats, the QR pattern was present in 14 per cent. Ventricular premature *beats also* occurred in cases of cor pulmonale and valvular heart disease (*mitral* and aortic) with congestive failure.

Autopsy was performed in 18 cases *with ventricular* premature beats *of the QR type* Of these 17 had myocardial infarction which extended to the septum *in 15* cases. In 7 of the autopsied cases septal infarction could be detected *electrocardiographically by the QR* pattern of the ventricular premature beats alone. In the two cases of myocardial infarction without septal involvement and in the case without myocardial infarction signs of right *cardiac enlargement* were present.

Right ventricular premature beats with a prominent initial R wave (RS complex) in the right precordial leads occurred in 2 cases with electrocardiographic evidence of septal infarction in the sinus beats and in 3 cases in which the diagnosis of septal infarction was confirmed at autopsy One of the last mentioned cases simultaneously showed a pathologic Q wave in the left precordial leads.

Left ventricular premature beats of the QR type in the right precordial leads and right ventricular premature beats of the RS type could

also be produced by mechanical stimulation of the endocardium during cardiac catheterization in cases of atrial septal defect.

The following conclusions are drawn (1) The QR patterns of ventricular premature beats in unipolar precordial leads have the same diagnostic significance as similar patterns in bundle branch block.

(2) The presence of the QR pattern of left ventricular premature beats in Leads V and V has only limited value in the diagnosis of myocardial infarction in cases with great dilatation of the heart.

3) The presence of a prominent initial R wave (RS complex) in right ventricular premature beats in Leads V, and V (the R wave diminishing in size from right to left across the precordium) is a supportive sign of septal infarction.

(4) In many instances infarction of the interventricular septum can be diagnosed solely by the unipolar precordial patterns of ventricular premat ure beats.

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ADDENDUM

Case reports

Case 1 (Fig. 1) T H. a 43-year-old male. Admitted Dec. 3 1961 died Dec. 9 1961.

The electrocardiogram on Dec. 4 shows several left VPB of the QRs pattern in Lead V_1 QRS pattern in Lead V_2 and qRS pattern in Lead V_3 No signs of septal damage appear in the sinus beats

Autopsy findings A recent infarction involved the posterior two-thirds of the interventricular septum the whole of the posterior wall and part of the lateral wall of the left ventricle. The necrosis also extended to a small area on the dorsal wall of the right ventricle Another fibrosing infarction interspersed with fresh areas, involved the apical portion of the anterior wall of the left ventricle and the anterior third of the interventricular septum. A fresh thrombus was present in the right coronary artery and an older atherosclerotic occlusion was found in the descending branch of the left coronary artery

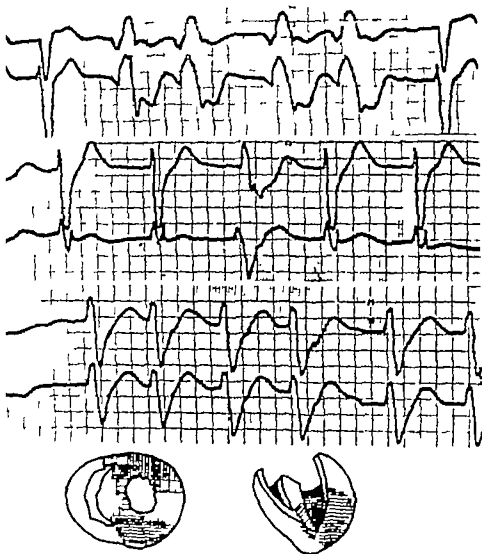


Fig 1

Case 1 (Fig. 1) T H a 43-year-old male. Admitted Dec. 3 1961 died Dec. 9 1961.

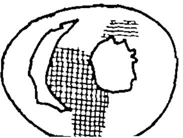
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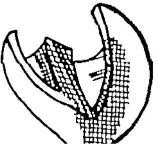
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V_1

V_2

V_3

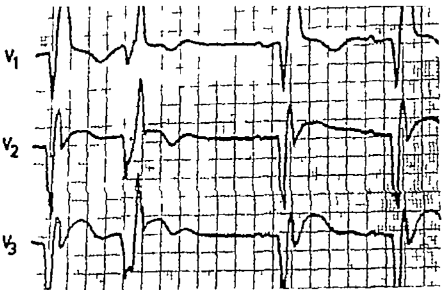


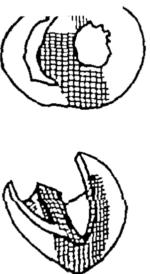


Case 2 (Fig. 2) M. O., a 55-year-old male. Admitted Nov 7 1961 died Nov 18, 1961.

The electrocardiogram on Nov 7 shows left VPB of the QR type in Lead V_1 and of the QRs type in Leads V_2 and V_3 The infarction patterns are also present in the sinus beats.

Autopsy findings A universal atherosclerosis with grave narrowing of both coronary arteries was observed. Thrombosis occurred in the anterior descending branch of the left coronary artery A recent infarction involved the anterior two-thirds of the interventricular septum and the apical half of the anterior wall of the left ventricle. An old scarring infarction was found in the posterobasal area of the left ventricle and an endocardial thrombus at the apex of the left ventricle Aseptic fibrinous pericarditis, edema of the lungs, acute congestion of the liver and spleen, and a recent infarction of the right kidney were further seen.





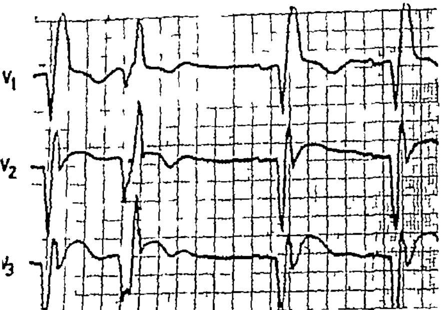
V1
V2

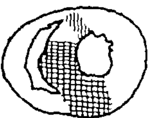
Aug 29 1960

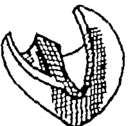
Case 3 (Fig. 3) J R. a 63-year-old male. Admitted Aug 28, 1960 died Aug. 30 1960

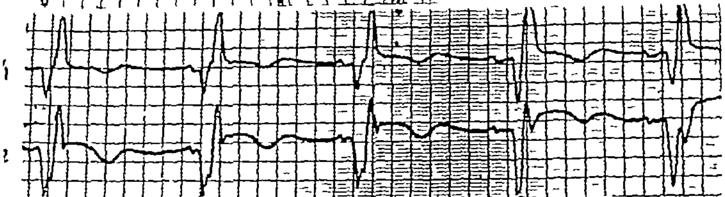
The electrocardiogram on Aug. 28 shows a left VPB of the QR type in Leads V_1 V_2 and V_3 The sinus beats also have the QR pattern in the same tracings (complete right bundle branch block and septal infarction) The electrocardiogram on Aug 29 shows the following the Leads V_1 and V_2 begin with a VPB of the QR type which coincides with the ascending P wave. The second and third beats are obviously also VPB which locate in the P R interval, the former slightly earlier than the latter Neither of these beats could hardly be considered fusion beats The fourth beat is probably a sinus beat. The fifth beat in Lead V_3 diff completely from a sinus beat and VP It is possible that both sinus beat a VPB activate the ventricles.

Autopsy findings A large fresh ne rotic area involved almost the who anterior wall of the left ventricle a the adjoining two-thirds of the inte ventricular septum. An older narro fibrotic zone was observed on the pos erobasal wall of the left ventricle Th anterior descending branch of the le coronary was thrombosed near i opening and the right coronary arter was almost occluded at a distance (3–4 cm. from its opening (due t atherosclerotic plaques) The heart wa considerably hypertrophied







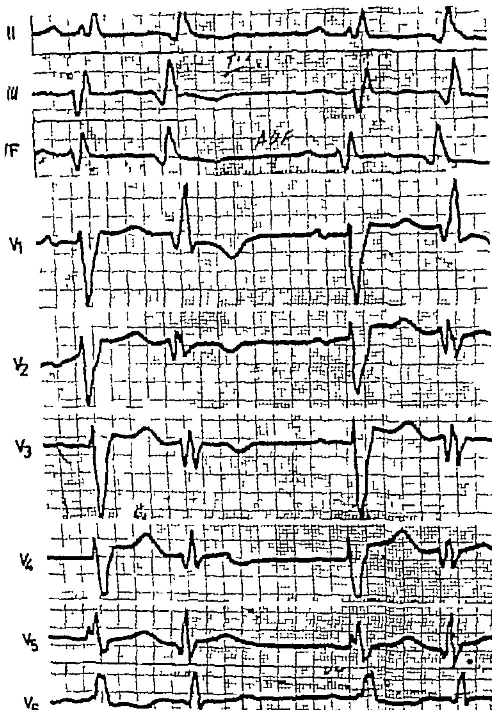


Aug 29 1960

Case 4 (Fig 4) A. H., a 74-year-old male. Admitted Jan. 27 1960 died Feb 13 1960

The electrocardiogram on Feb 4 shows a posterobasal (left?) VPB It has the following pattern In Leads V_1 V_5 and V_6 QRS V_2 V_3 and V_4 rSR S A complete left bundle branch block appears in the sinus beats with some rsR'S complexes in lead V_5 and rsR complexes in Lead V_6

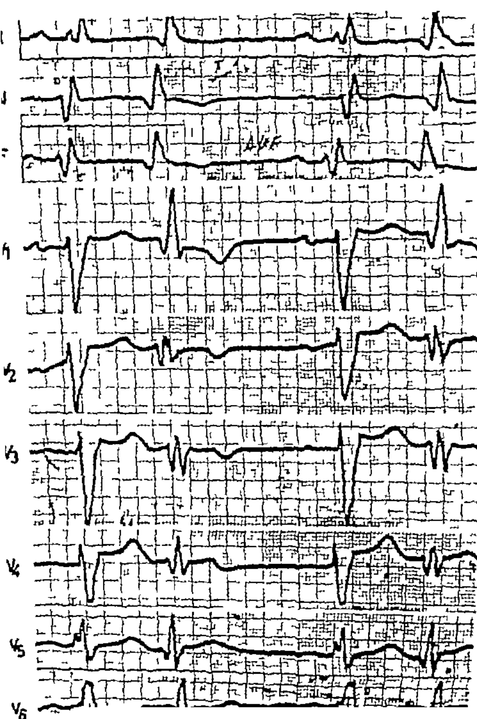
Autopsy findings A broad scarring infarction occurred at the posterior wall of the left ventricle extending to the apex and adjoining another narrower scarring infarction in the anteroseptal part of the left ventricle An atherosclerotic narrowing of both coronary vessels and thrombosis of the circumflex branch of the left coronary artery were found. Death was due to congestive heart failure


II
III
IF
V1
V2
V3
V4
V5
V6

Case 4 (Fig. 4) A. H. a 74-year-old male Admitted Jan 27 1960 died Feb 13 1960

The electrocardiogram on Feb 4 shows a posterobasal (left?) VPB It has the following pattern In Leads V_1 V_5 and V_6 QRS V_2 V_3 and V_4 rSR S A complete left bundle branch block appears in the sinus beats with some rsR'S complexes in lead V_5 and rsR complexes in Lead V_6

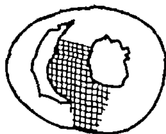
Autopsy findings A broad scarring infarction occurred at the posterior wall of the left ventricle extending to the apex and adjoining another nar rower scarring infarction in the antero-septal part of the left ventricle. An atherosclerotic narrowing of both cor onary vessels and thrombosis of the cir cumflex branch of the left coronary artery were found. Death was due to congestive heart failure


I
V2
V3
V4
V5
V6

Case 5 (Fig. 5) A. L. a 74-year-old male. Admitted Dec. 2 1960 died Dec. 6 1960

Electrocardiogram on Dec. 2 shows posterobasal left VPB of the QR type in Lead V_1 and *QRs* type in Leads V_2 and V_3 and qRS type in Lead V_4 Signs of infarction are also present in the sinus beats.

Autopsy findings A fresh necrotic area involved the two-thirds of the interventricular septum and the adjoining part of the anterior wall of the left ventricle. A grave atherosclerosis appeared in the coronary arteries, with thrombosis of the anterior descending branch of the left coronary artery There were some intervalvular adhesions between the aortic (semilunar) valves. The patient died of hemopericardium caused by rupture of the anterior wall of the left ventricle



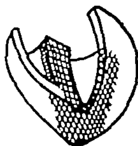


Fig 5

Case 6 (Fig. 6) A. H. a 62-year-old male. Admitted Nov 30 1961 died Dec. 1, 1961.

The electrocardiogram on Dec. 1 3 minutes before death, showed complete atrioventricular dissociation and transitory sinus block with ectopic atrial beats originating in the coronary sinus (negative P in Leads II, III and aVF) Left ventricular automatism was observed in unipolar precordial tracings. In addition, left VPB resemblig basic beats with the QR pattern occurred in Leads V_1 and V_2

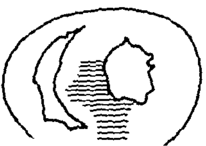
Autopsy findings Atherosclerotic narrowing of tortuous coronary vessels with thrombosis of the anterior descending branch of the left coronary artery were observed. An old scarring infarction involved the anterior part of the interventricular septum and apex, also extending to a narrow zone on the anterior wall of the left ventricle. An endocardial thrombus was found at the site of the scarring infarction. Hypertrophy and dilatation of both chambers of the heart, fatty infiltration of the heart and liver pulmonary congestion and edema and liver congestion were further found.

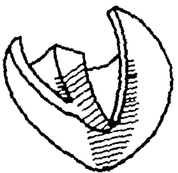
1

V_2

V_5

V_6





Case 6 (Fig 6) A. H. a 62-year-old male. Admitted Nov 30 1961, died Dec. 1 1961

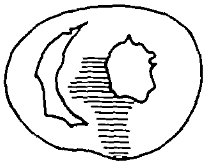
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Autopsy findings Atherosclerotic narrowing of tortuous coronary vessels with thrombosis of the anterior descending branch of the left coronary artery were observed. An old scarring infarction involved the anterior part of the interventricular septum and apex, also extending to a narrow zone on the anterior wall of the left ventricle. An endocardial thrombus was found at the site of the scarring infarction. Hypertrophy and dilatation of both chambers of the heart, fatty infiltration of the heart and liver pulmonary congestion and edema, and liver congestion were further found.

V_2

V_5

V_6



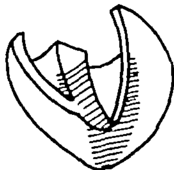
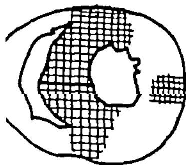


Fig 6

Case 6 (Fig. 6) A. H. a 62-year-old male. Admitted Nov 30 1961 died Dec. 1, 1961.

The electrocardiogram on Dec. 1 3 minutes before death, showed complete atrioventricular dissociation and transitory sinus block with ectopic atrial beats originating in the coronary sinus (negative P in Leads II, III and aVF) Left ventricular automatism was observed in unipolar precordial tracings. In addition left VPB resemblig basic beats with the QR pattern occurred in Leads V_1 and V_2

Autopsy findings Atherosclerotic narrowing of tortuous coronary vessels with thrombosis of the anterior descending branch of the left coronary artery were observed. An old scarring infarction involved the anterior part of the interventricular septum and apex, also extending to a narrow zone on the anterior wall of the left ventricle An endocardial thrombus was found at the site of the scarring infarction. Hypertrophy and dilatation of both chambers of the heart fatty infiltration of the heart and liver pulmonary congestion and edema and liver congestion were further found.



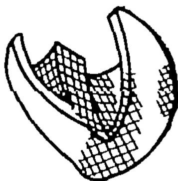
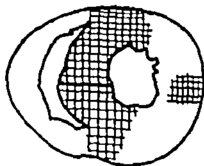


Fig 7

Case 7 (Fig. 7) J K. a 71 year-old male Admitted Oct. 16 1959 died Oct. 17 1959

The electrocardiogram on Oct. 17 shows a run of VPB resembling complete right bundle branch block with QR pattern in Leads V_1 and V_2 The form of the second VPB in the electrocardiogram differs from the other VPB in Leads V_1 and V_2 The origin of the VPB is obviously in the left ventricle, because in tracings not recorded simultaneously left VPB occurred in Leads V_5 and V_6

Autopsy findings Atherosclerotic thickening occurred in the coronary arteries with thrombosis of the anterior descending branch of the left coronary artery The left ventricle was hypertrophied A recent infarction involved the interventricular septum, also extending partly to the posterior and anterior parts of the left ventricle The lateral wall of the left ventricle was necrotic at the site of the biopsy but the width of the necrotic area could not be estimated. Pulmonary edema and congestion of the liver were noted.



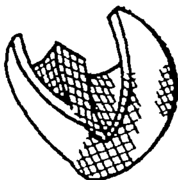


Fig 7

Case 8 (Fig. 8) H. L., a 52 year-old male Admitted Sept. 9 1960 died Sept. 23 1960

The *electrocardiogram* on Sept. 19 shows right VPB with pathologic Q wave in Leads II III, aVF V_4 The pattern of VPB resembles that of the *sinus beats (left bundle branch block)* Signs of infarction are present in the sinus beats also

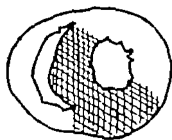
Autopsy findings A large fresh infarction involved the posterior and diaphragmatic wall of the left ventricle. An old fibrotic infarction was found in the *apical, anterior and partly also lateral* wall of the left ventricle extending to the adjoining part of the right ventricular wall and interventricular septum. *The circumflex branch of the left* coronary artery was thrombosed and the other coronary vessels narrowed as a result of an atherosclerotic process.

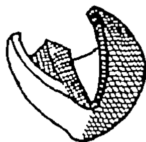


Case 9 (Fig. 9) A. M. a 72-year-old male Admitted Nov 19 1959 died Dec. 10 1959

The electrocardiogram on Nov 26 shows ventricular *tachycardia*. *There* appears a run of right VPB in which the initial R wave diminishes in size from right to left across the precordium A pathologic Q wave can be seen in Leads V_3 and the ventricular complex in Lead V_6 is of the rsR'S shape Signs of an anteroseptal infarction were present during the sinus rhythm.

Autopsy findings A recent infarction involved *the whole interventricular* septum and the anterior wall of the left ventricle Far-advanced atherosclerosis appeared in the coronary arteries with occlusion of the left coronary artery



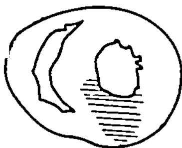


Case 10 (Fig. 10) A.K., a 54-year old male. Admitted March 21 1961 died May 5 1961

Several electrocardiograms showed left bundle branch block in the dominant rhythm without definite signs of myocardial infarction. The signs of a septal infarction were distinct however in the high precordial leads in the third intercostal space Right VPB appeared in several tracings.

The electrocardiogram on April 4 (Fig. 10) shows right VPB adjoining the ascendent part of P wave with a W-shaped complex in Lead V_1 a QRS complex in Lead V_4 and a qRs complex in Leads V_5 and V_6.

Autopsy findings An old scarring infarction was found in the anterior wall of the left ventricle, also involving the anterior part of the interventricular septum Both branches of the left coronary artery were almost occluded near their opening as a result of atherosclerosis. The patient died of pulmonary infarction.



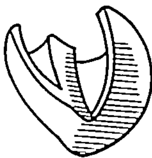


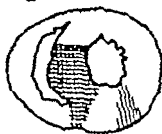
Fig 10

Case 11 (Fig. 11) N H., a 59-year old male. Admitted Oct. 12 1961 died Oct. 14 1961.

The electrocardiogram on Oct. 12 shows a relatively narrow VPB appearing after the P wave or adjoining it. The VPB has a QRS pattern in Lead V_4 and a QRs pattern in Lead V_5. The rS pattern occurs in Lead V_1 the rsR s pattern in Lead V_2 and the qrS pattern in Lead V_3. These VPB could be considered fusion beats. The infarction pattern is present in the sinus beats also.

Autopsy findings A recent infarction involved the interventricular septum and an older fibrotic infarction the apical anterior part of the left ventricle Atherosclerotic narrowing and occlusion were observed in both coronary arteries. Hypertrophy and dilatation of the left ventricle, pulmonary congestion and edema and acute liver congestion were further found, (and in addition chronic pyelonephritis with recent necrotizing papillitis)

avr
V2
V3
V4
V5

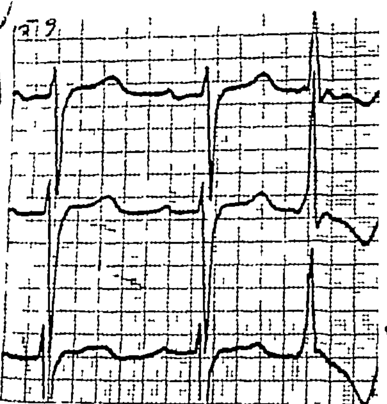




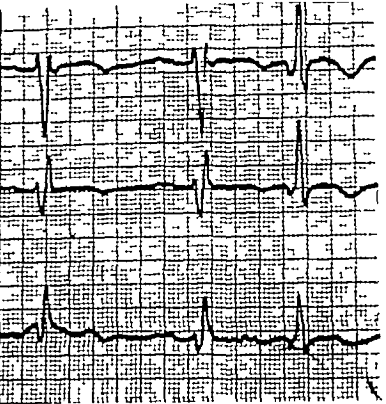
Case 11 (Fig. 11) N H., a 59-year old male Admitted Oct. 12 1961 died Oct. 14, 1961.

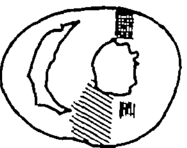
The electrocardiogram on Oct. 12 shows a relatively narrow VPB appearing after the P wave or adjoining it. The VPB has a QRS pattern in Lead V_4 and a QRs pattern in Lead V_5. The rS pattern occurs in Lead V_1, the rsR s pattern in Lead V_2 and the qrS pattern in Lead V_3. These VPB could be considered fusion beats. The infarction pattern is present in the sinus beats also.

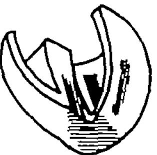
Autopsy findings A recent infarction involved the interventricular septum and an older fibrotic infarction the apical anterior part of the left ventricle. Atherosclerotic narrowing and occlusion were observed in both coronary arteries. Hypertrophy and dilatation of the left ventricle pulmonary congestion and edema, and acute liver congestion were further found (and in addition chronic pyelonephritis with recent necrotizing papillitis)



V4
V5
V6



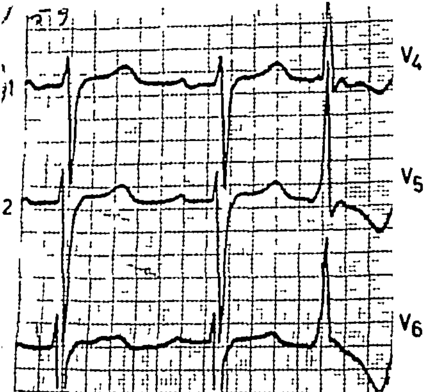


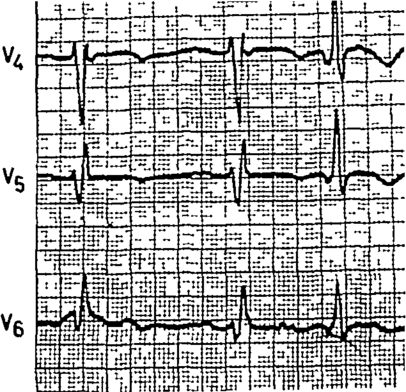


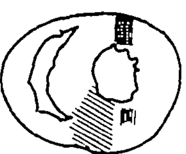
Case 12 (Fig. 12) Y S., a 39-year old male Admitted Nov 24 1959 died March 14, 1960

The electrocardiogram on Nov 25 shows a narrow VPB of the QRS type in Leads V_4 V_5, and V_6 The *origin of* the VPB may be in the upper posterior area of the left ventricle near the septum Definite signs of septal infarction are not seen in the sinus beats

Autopsy findings Atherosclerotic narrowing appeared in the coronary arteries. Recent infarction involved the inferior area of the posterior wall *of the left* ventricle. An old fibrotic infarction involved the antero-apical part of the interventricular septum and another old infarction a very narrow zone on the anterior wall of the left ventricle. The right ventricle was hypertrophied. An old, softened abscedding infarction in the lower lobe of the right lung, congestion of the lungs, liver and spleen and a fresh infarction in the left kidney were further found







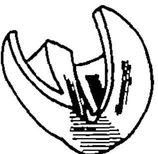


Fig. 19

Case 13 (Fig. 13) A. R., a 61 year-old female. Admitted Aug. 31, 1961 died Sept. 6 1961.

Electrocardiogram on Sept. 6 shows in the precordial leads the VPB origin ating in the left ventricle The VPB are of the QRs type in Leads V_3 V_4 and V_5 and of the QS type in Lead V_6 In the sinus beats there are no definite signs of septal infarction.

Autopsy findings A large scarring infarction partly mixed with fresh necrotic streaks involved the apex, the lower part of the anterior wall of the left ventricle and the anterior two-thirds of the interventricular septum. A big endocardial thrombus occurred at the apex of the left ventricle and a thrombus filled the anterior descend ing branch of the left coronary artery A thin fibrotic streak appeared in the posterior wall of the left ventricle. Hypertrophy of the heart, especially of the right ventricle and emphysematous lungs were observed. *The patient died* of pulmonary embolism

V_1

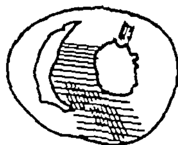
V_2

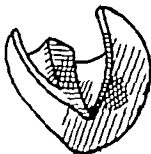
V_3

V_4

V_5

V_6





Case 13 (Fig. 13) A. R., a 61 year-old female Admitted Aug. 31, 1961 died Sept. 6 1961.

Electrocardiogram on Sept. 6 shows in the precordial leads the VPB originating in the left ventricle. The VPB are of the QRs type in Leads V_3 V_4 and V_5 and of the QS type in Lead V_6 In the sinus beats there are no definite signs of septal infarction.

Autopsy findings A large scarring infarction partly mixed with fresh necrotic streaks involved the apex the lower part of the anterior wall of the left ventricle and the anterior two-thirds of the interventricular septum. A big endocardial thrombus occurred at the apex of the left ventricle and a thrombus filled the anterior descending branch of the left coronary artery A thin fibrotic streak appeared in the posterior wall of the left ventricle. Hypertrophy of the heart especially of the right ventricle and emphysematous lungs were observed. The patient died of pulmonary embolism.

V_1

V_2

V_3

V_4

V_5

V_6



Fig. 13

Case 14 (Fig. 14) A. K. a 52 year old female Admitted Aug. 14 1960 died Sept. 2, 1960

The electrocardiogram on Sept. 1 shows a left VPB with the QR pattern in Lead V_1 Signs of septal infarction are lacking in the sinus beats in the precordial leads.

Autopsy findings A recent infarction involved the posterior wall of the left ventricle also extending to the lateral wall of it. The endocardial surface of the anteroseptal portion of the left ventricle as well as the lateral wall showed areas with fibrotic streaks mixed with fresh necrotic tissue. Several endocardial thrombi were found in the left ventricle and auricle. Both coronary arteries were obliterated at some points by atherosclerotic plaques and the circumflex branch of the left coronary artery contained a fresh thrombus.

III

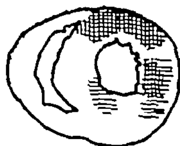
VR

VL

VF

V_1

V_2



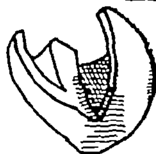


Fig 14

Case 15 (Fig. 15) P L. a 38-year-old male. Hospitalized several times from Jan. 1961 died July 30 1961.

The electrocardiogram on Jan. 17 1961, shows a left VPB with the qR pattern in Leads V_1 and V_2 No definite signs of septal infarction in the sinus beats.

Autopsy findings A malignant hepatoma was found with widespread metastases in mediastinal lymph nodes etc., collapsing the lower and part of the middle lobe of the right lung. The heart, especially its right ventricle was hypertrophied. Aneurysmal bulging appeared at the apex and fibrotic streaks in the posterobasal part of the left ventricle. The basal part of the interventricular septum showed a fibrotic chord too

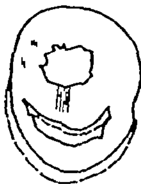
V_1

V_2

V_5

V_6





Case 16 (Fig. 16) H. K. a 64-year old female Admitted Aug. 5 1961 died Aug 6 1961

The electrocardiogram on Aug. 6 shows a left VPB with the qR pattern in Lead V_1 The dominant rhythm shows atrial fibrillation.

Autopsy findings An infarction was found in the postero-apical wall of the left ventricle. The interventricular septum was intact. The mitral valve was stenotic and the right ventricle greatly enlarged

Comment The qR pattern of the VPB in Lead V_1 may be caused by the right ventricular enlargement due to mitral stenosis and not by myocardial infarction.

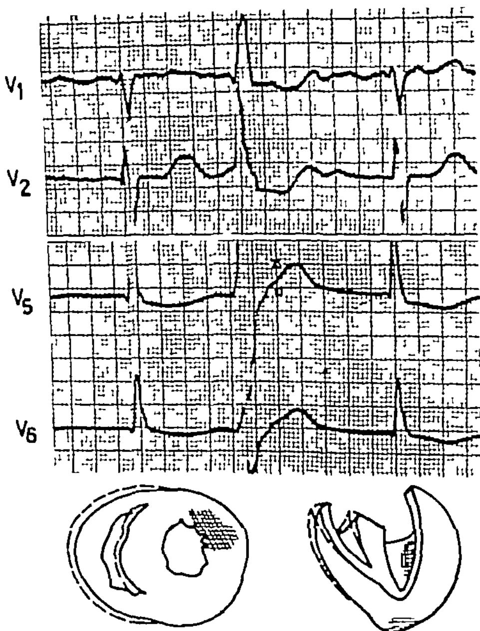


Fig. 16

Case 16 (Fig. 16) H. K. a 64-year old female Admitted Aug. 5 1961 died Aug. 6 1961

The electrocardiogram on Aug. 6 shows a left VPB with the qR pattern in Lead V_1 The dominant rhythm shows atrial fibrillation.

Autopsy findings An infarction was found in the postero-apical wall of the left ventricle The interventricular septum was intact. The mitral valve was stenotic and the right ventricle greatly enlarged.

Comment. The qR pattern of the VPB in Lead V_1 may be caused by the right ventricular enlargement due to mitral stenosis and not by myocardial infarction.

I

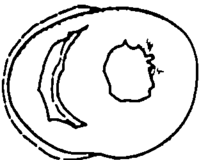
II

aVL

aVF

V_1

V_2



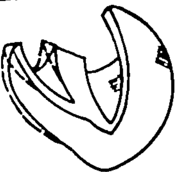


Fig 17

Case 17 (Fig. 17) K. V., a 66-year old male. Admitted Nov 12, 1960 died Nov 18, 1960.

The electrocardiogram on Nov 14 shows left VPB with the following patterns. in Lead V_1 QRs and rSRs and in Lead V_2 rsr'S and RS Changes characteristic of anterolateral ischemia were seen in the sinus beats.

Autopsy findings. A chronic rheumatic mitral insufficiency with hypertrophy and dilatation of both chambers and signs of left and right heart failure was found. A stenosing atherosclerosis appeared in the coronary arteries and small endo-myocardial cicatrices on the posterior and lateral walls of the left ventricle. The patient died of pulmonary embolism.

Comment In this case we believe *that the QRs pattern of VPB in Lead* V_1 was a consequence of the great enlargement of the right ventricle.

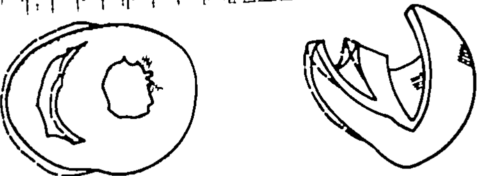


Fig. 17

Case 18 (Fig 18) O P., a 74-year old male. Admitted March 21 1959 died March 28, 1959

The VPB in Lead V_1 is of the QR type as are also the sinus beats. The VPB originates in upper and posterior portion of the left ventricle resembling right bundle branch block.

Autopsy findings The right ventricle was considerable dilatated and the pulmonary conus rounded. The right auricle contained thrombi attached to the endothelium. The circumflex artery was occluded 4 cm. from its opening. The lumina of the other coronary arteries were quite patent in spite of sclerosis, and the signs of myocardial infarction were absent. Stasis occurred in the liver *Cavernous pulmonary* tuberculosis, pleural adhesions and pulmonary emphysema were also found.

Comment This case demonstrates that a left VPB of the QR pattern may occur in the right precordial leads without the presence of myocardial infarction in right cardiac enlargement.

I

V1

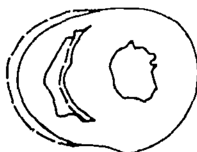
V2

V3

V4

V5

V6



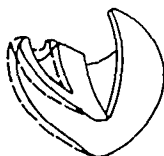


Fig 18

[illegible]

[illegible] findings. A recent [illegible] [illegible] involved most of the [illegible] [illegible] ventricle also [illegible] [illegible] [illegible] of the [illegible] [illegible] and [illegible] lateral [illegible] [illegible] The [illegible] [illegible] [illegible]

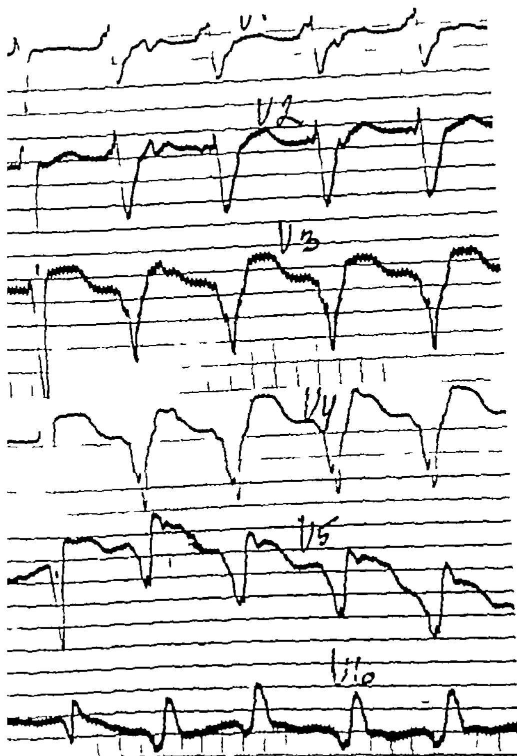


Fig 19

Case 19 (Fig. 19) J P a 55-year-old *male. The patient suffered from massive* myocardial infarction (SGOT 491 units) The electrocardiographic evidence of damage of the interventricular septum and anterolateral wall of the left ventricle is recognizable in the sinus beats as well as in the right VPB. *The diagnostic pattern of these VPB is* of the Rs type in Lead V_1 rS type in Lead V_2 QS type in Leads V_3 and V_4 Qrs type in Lead V_5 and QR type in Lead V_6

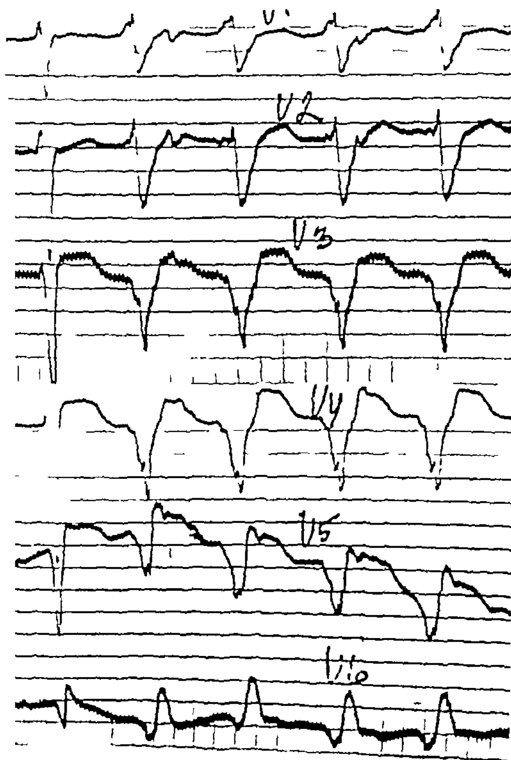


Fig 19

Case 20 (Fig 20) P R. a 57 year-old male. Admitted Aug. 21 1959 died *Aug 23 1959*

The electrocardiogram on Aug. 21 shows a VPB resembling left bundle branch block but with the special characteristic of a prominent initial R wave in Lead V_1 The R wave in Lead V_1 is clearly higher than the R in Leads V_2 and V_3

Autopsy findings A recent infarction involved most of the anterior wall of the left ventricle, also extending to the ventral halves of the interventricular septum and the lateral wall of the left ventricle. The coronary arteries were atherosclerotic and almost obliterated — especially both branches of the left coronary artery

I

II

III

aVR

aVL

aVF

V_1

V_2

V_3

V_4

V_5

V_6

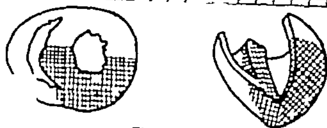


Fig 20

Case 20 (Fig. 20) P R., a 57 year-old male Admitted Aug. 21, 1959 died Aug. 23 1959

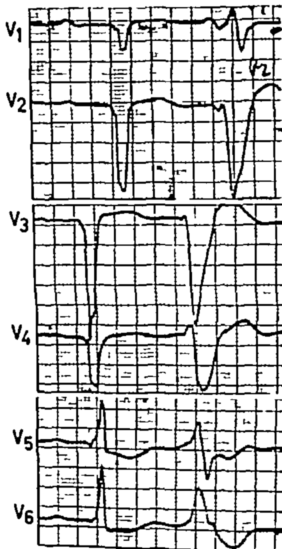
The electrocardiogram on Aug. 21 shows a VPB resembling left bundle branch block but with the special characteristic of a prominent initial R wave in *Lead* V_1 *The R wave in Lead* V_1 is clearly higher than the R in Leads V_2 and V_3

Autopsy findings A recent infarction involved most of the anterior wall *of the left ventricle also extending to* the ventral halves of the interventricular septum and the lateral wall of the left ventricle. The coronary arteries were atherosclerotic and almost oblit *erated — especially both branches of* the left coronary artery

Oct 5 1959



Oct.30.1959



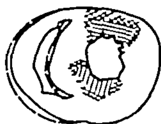




Fig 21

Case 21 (Fig 21) L. A. a 50-year old male. *Admitted Oct. 3 1959 died* Nov 4, 1959

The electrocardiogram on Oct. 5 shows a right VPB in which the R in Lead V_1 is smaller than the R in Lead V_2 *In the tracing recorded on Oct. 30* a right VPB also occurs after the P wave or adjoining it. The R wave in this VPB is prominent in Lead V_1 and clearly higher than those in Leads V_2 *to* V_4 *Signs of myocardial infarction* are present in the sinus beats — QS pattern in Leads V_1 to V_3 qrS pattern in Lead V_4 and qR pattern in Leads V_5 and V_6

Autopsy findings A far-advanced stenosing atherosclerosis of both coronary arteries and a scarring infarction at the anteroseptal margin and apex of the left ventricle were found. A similar *infarction also occurred on the* posterior wall of the left ventricle extending from the base to the apex. The fibrotic areas were mixed with recent minor necrotic patches. Endocardial *thrombi were observed in the* left ventricle and in the right atrium. The right ventricle was dilatated. The lungs and liver showed changes characteristic of congestive heart failure *and a recent* infarction appeared in the lower lobe of the right lung.

Comment The possible initial negativity of the VPB in Leads V_1 to V_3 may be caused by the weak persistent right to-left forces in *the septum*. The right ventricular enlargement may participate in producing the high R in Lead V_1



Fig 22

Case 22 (Fig. 22) O R. a 10-year old boy suffering from atrial septal defect.

During cardiac catheterization the catheter slipped through the atrial septal defect into the left atrium and entered the left ventricle The blood pressure was at the systemic level and the blood samples showed a maximal oxygen saturation.

The VPB were recorded in Leads V_{4r} and and V_6 when the catheter was presumably located against the septal wall of the left ventricle The second beat is a mechanically produced *left* VPB of the QR type in V_{4r} and of RS type in Lead V_6 beginning in the ascendent part of the P wave (The upper tracings in the figure) In the lower tracings left VPB of the QR type occur but here they are located in the P R interval much after the P wave The last VPB could be considered a fusion beat Incomplete right bundle branch block appears in the sinus rhythm.

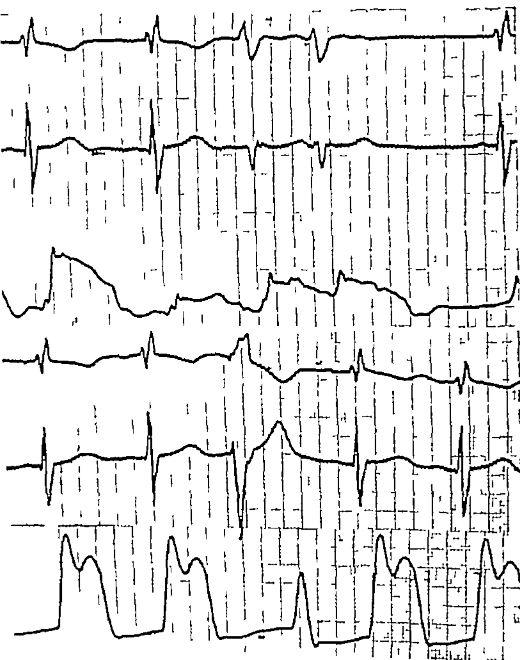


Fig 23

Case 23 (Fig 23) L. K., an 11 *year* old girl suffering from atrial septal defect.

The VPB were recorded in Leads V_{4r} and V_6 when the catheter was located in the lower part of the right ventricle near the septum, and on with drawal of the catheter from the ven tricle (the upper tracings in the fig ure) The VPB are of the RS shape in Lead V_{4r} and of the Qrs and rSr shape in Lead V_6 The electrode in Lead V_6 was obviously slightly to the left of the septum level. The left VPB were obtained after the catheter had passed the atrial defect and left atrium and was presumably located against the septal wall of the left ventricle (systemic blood pressure and complete oxygen saturation) The mechanically produced VPB is of the qR shape in Lead V_{4r} and rS shape in Lead V_6 Incomplete right bundle branch block appears in the sinus rhythm (the lower tracings in the figure)

ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 386

THE EFFECTIVENESS OF ACTIVATORS IN CLOT LYSIS WITH SPECIAL REFERENCE TO FIBRINOLYTIC THERAPY

A New Method for Determination of Preformed Clot Lysis

BY

SVERRE BLIX

Accompanies Vol. 17

OSLO 1962

THE EFFECTIVENESS OF ACTIVATORS IN CLOT LYSIS WITH SPECIAL REFERENCE TO FIBRINOLYTIC THERAPY

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FROM THE INSTITUTE FOR THROMBOSIS RESEARCH, UNIVERSITY HOSPITAL
(HEAD: P. A. OWREN, M.D.), RIKSHOSPITALET, OSLO, NORWAY

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SVERRE BLIX

OSLO 196

From the Institute for Thrombosis Research, University Hospital (Head: P. A. Owren, M. D.)
Rikshospitalet, Oslo, Norway

The Effectiveness of Activators in Clot Lysis, with Special Reference to Fibrinolytic Therapy

A New Method for Determination of Preformed Clot Lysis

By
Sverre Blix

Introduction

Human plasma contains a fibrinolytic system. The purpose of thrombolytic therapy is to dissolve fibrin deposits in the vascular bed. This may be achieved by supplement of the fibrinolytic enzyme plasmin or by activation of the pre-existing fibrinolytic system by means of activators. Numerous reports about the use of fibrinolytic agents on patients have been published. The lack of knowledge about the mechanism of clot lysis however has usually made the administration precarious and the effect of treatment has never been evaluated by a satisfactory trial of comparable control groups of untreated patients.

Experimental clots have been prepared in humans for the study of induced fibrinolysis (Johnson & McCarty 1959) but for practical reasons this is not as a rule possible. Animals are less suitable for such experiments because their fibrinolytic systems differ in many respects from that in humans. Therefore one is restricted to drawing conclusions from *in vitro* experiments with human blood. It is difficult however to provide conditions comparable to those *in vivo* because of the great differences always existing between clots and thrombi. Methods for registration of fibrinolysis on the surface of preformed human clots have previously been reported (Alkjaersig *et al* 1959, Kaulla 195[illegible], Fischbacher 1961). By their method Alkjaersig *et al.* (1959) showed that in fibrinolytic therapy plasminogen activators seem more effective than plasmin. So far streptokinase and urokinase have been tried in thrombolysis but problems related to the intensity and duration of treatment are still under discussion.

The present experimental study con

(Norges almenvitenskapelige forskningsråd)
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From the Institute for Thrombosis Research, University Hospital (Head: P. A. Owren, M. D.)
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Artificial clots have been prepared in humans for the study of induced fibrinolysis (Johnson & McCarty 1959) but for practical reasons this is not as a rule possible. Animals are less suitable for such experiments because their fibrinolytic systems differ in many respects from that in humans. Therefore one is restricted to drawing conclusions from *in vitro* experiments with human blood. It is difficult however to provide conditions comparable to those *in vivo* because of the great differences always existing between clots and thrombi. Methods for registration of fibrinolysis on the surface of preformed human clots have previously been reported (Alkjaersig *et al.* 1959; Kaulla 1959; Fischbacher 1961). By their method Alkjaersig *et al.* (1959) showed that in fibrinolytic therapy plasminogen activators seem more effective than plasmin. So far streptokinase and urokinase have been tried in thrombolysis but problems related to the intensity and duration of treatment are still under discussion.

The present experimental study con-

sisting of three main sections is comprised of supplementary investigations regarding the mechanism of clot lysis.

1 The first problem was to separate the activator which occurs in blood during exercise (Biggs *et al* 1947) and study some qualities related to this spontaneous activator The activator was found capable of being completely adsorbed to fibrin during coagulation.

2 A simple and reliable method has been worked out for the study of fibrinolysis of preformed clots.

3 In the final section the purpose has been to study the possibility of utilizing a selective adsorption of activators to fibrin in thrombolytic therapy to estimate the intensity of treatment required in thrombolytic therapy to evaluate the importance of individual variations in inhibitors and antibodies and to study the effect of the inhibitor epsilon aminocaproic acid.

Materials and methods

MATERIALS

Ammonium sulph t A saturated, neutralized sol tion of ammonium sulphate was used.

Anticoagulant 1) Sod um cit te dihydrat 3 13 gm per cent 2) potass um oxalat monohydrat 2.5 per cent 3) heparin (A. L. Oslo Norw y) of rying concentrations in sal ne

Buffer A mod fied eronal buff (pH 7 35 nd ionic trength 0 154) was prepared by m xing sodium d eth l barbiturat 11 75 gm sod m chloride 14 67 gm 0 1 N HCl 430 ml and d t lled water t 2 000 ml (Owren 1947)

C al um hloride was d luted in saline from 50 mM aqueous stock sol tion t the desired concentrations.

Epsilon-am no-caproic acid. Epsilon-aminokapronsyra ach ial contain g 50 ml of 10 per cent sol tion — w kindly supplied by Kabi A B Stockholm, Sweden. The sol tion was diluted w th buffer t the desi ed concentrations.

Fibrinogen 1) Human fibrinogen. Fibrinogen (Kabi A.B Stockholm, Sweden) one bottle containing 1 gm lyophilized fibrinogen and 1 gm sodium chloride. The content was dissol d to the desired concentrations in distilled water and buffer to ionic strength 0 15 and used within a few hours. The clottability was about 95 per cent. 2) Bovine fibrinogen f r the fibrin plates as prepared by N Gröndahl Spånga, Sweden. The fibrinogen clott bility was about 97 per cent. It was st red in aliquots at —20 C in a 1.2 per cent sol tion n buffer and was d luted t 0 12 per cent n buffer after thawing

Both fibrinogen preparations were contaminated with plasminogen.

Sod m c bonate was used in 0.1 per cent stock solution

Spontaneous activ tor see p 00

Streptok nase 1) Varidase (Lederle Laboratories, New York, U.S.A.) containing 20,000 Christensen units of streptokinase and 5 000 unit of streptodornase pe ial. The material was dissol ed and dil ted t the desired concentra tions in buffer and used for preparation of the streptokinase-proacti ator solution only 2) Kabikinase 250 000 Christensen un ts per ial was kindly upplied by A.B Kabi (Stockholm, Sweden) The material was dissol ed in buffer to 36 000 nits per ml nd tored aliquots at —20 C The material was thaw d and diluted t the desired concentrations in buffer before use. Kabikinase has been used all the periment xcept f the preparation of streptokinase-pro act at

To oid adsorpt on of treptokinase t glass lusteroid t bes were used (Lassen 1958 I Blix 1962)

St eptokinase proactivator was p epared in the following w y The euglobulin sol tion from normal plasma (precipitated at pH 5 9 in propor on one to ninetee w th acetic acid) was tored t —20 C After thawing the eugl bulin solution clotted pontaneously at 37 C The fib in was removed and the proacti tor concentration the d fibrinated sol tion was 41 of that plasma This sol tion was diluted with buffer n proportion one t twenty four and m xed w th an equal olume of treptokinase

(Varidase®) containing 200 units per ml. In accordance with experiments previously described, the solution contained an excess of proactivator for streptokinase-preactivator formation (Blix 1962). It was stored in aliquots at −20 C and quickly thawed before use. The units refer to its streptokinase content.

Lusteroid tubes were used to avoid adsorption to glass surface.

Thrombin. 1. Human thrombin was prepared by the method described by Hjort and Stormorken (1957). The thrombin solution, 80 NIH units per ml, was stored in aliquots at −20 C and diluted to the desired concentrations in buffer after thawing.

2. Bovine thrombin was used for the fibrin plates only. "Topostasin" (Roche, Switzerland) containing 3 000 NIH units per vial was dissolved in buffer to 150 units per ml, stored in aliquots at −20 C and diluted after thawing to the desired concentration in buffer. Fresh solution was prepared every week.

Both thrombin preparations were contaminated with plasminogen.

Urokinase. Urokinase Quality 1, was kindly supplied by Leo Pharmaceutical Products (Ballerup, Denmark). Each vial contained 48 mg (4,200 Ploug units per mg). The substance was dissolved in saline to 2,000 units per ml, stored in aliquots at −20 C and diluted to the desired concentrations in buffer after thawing.

METHODS

Collection of blood. 1. Blood and anticoagulant were mixed in proportion nine to one and immediately centrifuged at 4 C for 30 min. at 2,500 r.p.m. (1 400 G) for platelet-poor plasma. For our experiments citrated platelet-poor plasma was collected before breakfast, except where otherwise stated. The plasma was immediately pipetted off, and, if not used at once, it was stored in aliquots at −20 C and thawed quickly before use.

2. Platelet-rich plasma was obtained by centrifuging the blood at 4 C for 30 min. at 600 r.p.m. (60 G), and used at once.

3. For lipemic plasma the blood was collected three hours after a breakfast rich in fat (including ½ l of cream).

4. Serum was obtained in three different ways: a) Serum. Blood collected before breakfast was allowed to coagulate spontaneously during 15 min. at room temperature. Then it was centrifuged as for platelet-poor plasma and the serum pipetted off. b) Saline serum. Nine parts of blood and one part of saline were mixed and prepared as for normal serum. c) Citrated serum. Nine parts of blood were left to coagulate for 15 min. at room temperature. Then one part of citrate was added and the blood prepared as for normal serum. All the sera were used immediately or stored in aliquots at −20 C and quickly thawed before use.

5. Platelet-poor red blood cell suspension was prepared by centrifuging citrated blood at 1 100 r.p.m. (270 G) for 10 min. The red cells were washed in double the volume of saline, the suspension was centrifuged at 1 100 r.p.m. for 10 min. and the saline pipetted off. The red cells were further centrifuged at 2,500 r.p.m. (1 400 G) for 10 min. and the remaining saline pipetted off. The red cells were now mixed with an equal volume of buffer and the suspension was ready for use. Fresh suspension was prepared every second day and stored in a refrigerator.

Colorimetric determinations were performed in a Ljungberg colorimeter (Lars Ljungberg & Co., Stockholm, Sweden).

Euglobulin fraction from citrated plasma was prepared as described by Blix (1961 II).

Fibrinogen determinations were performed as previously reported (Blix 1962).

Fibrinolytic investigations. 1) Fibrin plates were prepared and used as described by Astrup and Müllertz (1952) and Lassen (1952). The heated plates were kept at 85 C for one hour. All tests were performed in triplicate. In the present tests the sensitivity to proteolytic enzymes on the standard and the heated plates was approximately the same. 2) The clot lysis experiments have been described in detail in the text. They were all performed at 37 C, as a rule in duplicate. The complete clot lysis was recorded as previously described (Blix 1962).

Immunological determinations (kindly carried out by Dr Trond Rosenlov) were performed by the agar gel diffusion technique (Ouchterlony 1958).

sisting of three main sections is comprised of supplementary investigations regarding the mechanism of clot lysis.

1 The first problem was to separate the activator which occurs in blood during exercise (Biggs *et al* 1947) and study some qualities related to this spontaneous activator The activator was found capable of being completely adsorbed to fibrin during coagulation.

2. A simple and reliable method has been worked out for the study of fibrinolysis of preformed clots.

3 In the final section the purpose has been to study the possibility of utilizing a selective adsorption of activators to fibrin in thrombolytic therapy to estimate the intensity of treatment required in thrombolytic therapy to evaluate the importance of individual variations in inhibitors and antibodies and to study the effect of the inhibitor epsilon aminocaproic acid

Materials and methods

MATERIALS

Ammonium sulphat A saturated neutralized sol tion of ammonium sulphat was used.

Anticoagulant 1) Sodium citrate dihydrat 3 13 gm per cent 2) potassium oxalat monohydrat 2.5 per cent 3) heparin (A. L. Oslo Norw) of rying concentrations in sal ne.

Buffer A mod fied eronal buff (pH 7.35 nd ionic st ength 0 154) was p epared by mixing sod um dieth l barb tu t 11 75 gm sod m chlorid 14 67 gm 0 1 N HCl 430 ml and distilled w ter to 2,000 ml (Owren 1947)

Calcium hloride was d luted in saline from 50 mM aqueous stock sol tion t the desired concentr tions.

Epsilon-amino-caproic acid. Epsilon-amino-kapronsyra each ml contains g 50 ml of 10 pe ce t sol tion – was kindly supplied by Kabi A.B Stockholm, Sweden. The sol tion was diluted with buffer to the desired concentrations.

Fibrinogen. 1) Human fibrinogen. F brinog (Kabi A.B. Stockholm, Sweden) one bottle containing 1 gm lyophilized fibrinogen and 1 gm sodium chloride. The content was dissolved to the desired concentrations in distilled ater and buffer to i nic strength 0 15 nd used within a few hours. The clottab lity was bout 95 per cent. 2) Bov ne fibrinogen for the fibrin plat as prepared by N Grondahl, Spå ga, S eden. The fibrinogen clottability was about 97 per cent. It was stored in aliquots at —20 C in a 1 2 per cent solution in buffer and was diluted t 0.12 per cent in buffer after thaw ng

Both fibrinogen preparations were contaminated with plasminogen.

Sodium carbonat was used n a 0.1 per cent stock solution.

Spontaneous activator see p 00.

Streptokinase 1) Varidase (Lederle Laboratories New York U S.A) conta ning 20,000 Christensen units of streptokinase and 5 000 units f streptodornase per ml. The material was dissolved nd diluted t the desired concent ations in buffer nd used for preparation of the streptokinase-proacti at solution only 2) Kabikinase 250 000 Christensen u its per ml was kindly supplied by A.B Kabi (Stockholm, S eden) The material was dissol ed n buffer to 36 000 units per ml and t red aliquots at —20 C The material was thaw d and diluted t the desired concentrations n buff r before use Kabikinase has been used i all the periments except for the preparation f streptokinase-proacti at r

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("Varidase") containing 200 units per ml. I accordance with experiments previously described, the solution contained an excess of proactivator for streptokinase-proactivator formation (Blix 1962). It as stored in aliquots at −20 C and quickly thawed before use. The units refer to its streptokinase content.

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Immunological determinations (kindly carried out by *Dr. Trond Rensdorf*) were performed by the agar gel diffusion technique (Ouchterlony 1958).

Proactivator determinations were made as previ-ously described (Blix 1962).

Spectrophotometrical determinations were made in a Beckman spectrophotometer (Beckman Instruments, München Germany)

An *in vitro* method for registration of the fibrinolysis of a preformed standard clot

1 The principle of the method

In plastic tube the fibrinolytic agent dissolves a preformed standard clot from the rface The plastic t be rotates at 37°C and the dissolution of the clot has been observed by determination of hemoglobin in released red cells from the clot (see below)

2 The equipme t (Fig 1)

Plastic tubes 15 × 37 mm w th plastic stoppers.

ii Glass test tubes 10 × 60 mm w th rubber toppers.

ii An automatic record play r (Philips) placed at an angle f 60 in a thermostat cabinet at a constant temperature of 37 C and rotating at 16 r p m.

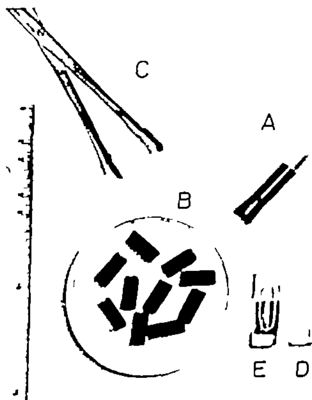
v F rceps protected w th adhesiv plast r on the branches.

3 The liquid

The liquid in the plastic tubes consisted of 2.8 ml buffer in which the test material as dissolved or f 2.1 ml plasma or serum t hich was added the test material dissolved in 0.7 ml buffer

4 The standard clot

The standard clots were prepared in glass test tubes t room temperature The tubes were turned psid down three times before coagulation occurred for an even distribution of the red cells. After the third time the t bes were left pside down (Fig 1) After twenty minutes the clot as caref lly transferred to the saline and was eady f use.



F g 1 The equ pment f r the standard clot t m
A. The standard lot in the glass t st t be af er coagulation
B Ten tandard lot saline fter emoval from the test tubes
C Forceps for the t ansf of clot from saline t the plastic t be
D F Plastic t bes used in he est system, one em pty and on filled w th liq id and the k

A. The purified clot:

0.6 ml human fibrinogen (100 mg)

0.4 ml red blood cell suspension (platelet poor)

0.2 ml thrombin (2.4 N.I.H. units per ml). The fibrinogen clotted within 1 / min. Platelets in the clot were avoided because clot retraction made the observations unreliable. (For preparation of red cell suspension, see Methods: collection of blood, p. 00).

B. The plasma clot

0.4 ml citrated or oxalated plasma

0.4 ml red cells (in platelet poor suspension)

0.4 ml calcium chloride (30 mM).

The clotting time varied from 2–4 min., depending on the plasma used.

3. Procedure

The liquid was pipetted into the plastic tubes and the standard clot transferred by means of the forceps. The total volume of the lysis system was always 4 ml. The tubes were placed on the automatic record player at 37 C and as the clot lysed under the influence of fibrinolytic agents, red blood cells were released and suspended in the surrounding liquid. Because of the even distribution of red cells in the clot, the percentage of cells released during a certain time corresponds to the percentage of the clot lysed. The clots kept their normal shape until completely dissolved. As a rule the tests were made in duplicate and never more than two samples were taken from one tube for examination.

4. Determination of clot lysis

The percentage of red cells released into the liquid was recorded through hemoglobin determination and interpolation on a reference curve. 0.2 ml of the liquid was removed and mixed with 3.5 ml sodium carbonate. The red cells hemolysed within a few seconds and the transmission in the colorimeter was measured.

The reference curve was made by mixing all materials in proportions as if 0, 25, 50, 75 and 100 per cent of the clot had been lysed. The composition of these mixtures is reported in Table 1. 0.2 ml of the mixture was removed and mixed with 3.5 ml sodium carbonate and the transmission in the colorimeter was measured. The reference curve was drawn on the basis of the values obtained, as shown in Fig. 2.

A new curve was prepared every day.

7. Standard deviation

In the system the spontaneously released cells never exceeded 6 per cent in the course of six hours or 12 per cent in the course of 20 hours.

The standard deviation for 12 parallel tests was calculated as described before (Blix 1962). In this case the fibrinolytic agent used was streptokinase-proactivator which lysed 20 per cent of the clot within half an hour and 66.5 per cent within one hour. The standard deviation after half an hour was 1.8 per cent and after one hour 1.4 per cent; the coefficient of variation 9 per cent and 2.1 per cent respectively.

8. Experiments

All experiments according to this method are reported in the final section. The standard clot prepared from fibrinogen and with buffer for liquid is referred to as the purified standard clot system; the clot prepared from plasma and with

Table 1. Composition of the solutions for determination of the reference curve in the plasma standard clot system. In these mixtures citrate or plasma are present in sufficient amounts to avoid clotting.

Per cent of the clot lysed	From the clot (ml)			The liquid (ml)	
	Red blood cell suspension	$CaCl_2$	Plasma	Plasma	Buffer
100	0.4	0.4	0.4	2.1	0.7
75	0.3	0.3	0.3	2.1	0.7
50	0.2	0.2	0.2	2.1	0.7
25	0.1	0.1	0.1	2.1	0.7
0	0	0	0	2.1	0.7

Pr actinat deterne nat ons were made as prev ously described (Blix 196_).

Spectrophotometrical determinat ons were made in a Beckman spectrophotometer (Beckman Instruments, München, Germany).

An *in vitro* method for registration of the fibrinolysis of a preformed standard clot

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F rceps protected w th adhesi plaster on the branches.

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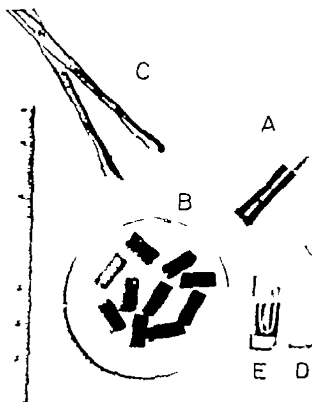


Fig 1 Th eq pmen f r the stan d rd lot sten

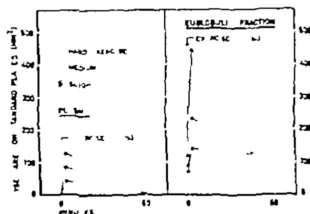
A The standard lot he glass test t be t ng lat on

B Ten st ndard k sal ne af er remo al from h est bes.

C Forceps f r he ansf lots from sal ne he plas ic bes

D) I Plastic bes used he t stem, one empty and one filled with liquid and he l t

Fig. 3. The same subject was on different day exposed to three minutes of slight, medium or hard exercise (see text). The figure presents the fibrinolytic activity in plasma and in the corresponding euglobulin fraction of plasma before and immediately after the exercise and after one hour in bed, as tested on standard fibrin plates.



ator from the fibrin plat product and the plasmin-plasminogen by means of ammonium sulphate precipitation. The buffer solution was immersed in an ice bath immediately after the complete dissolution of the fibrin. Ice-cold saturated ammonium sulphate final concentration of 30 per cent was added. The precipitate was centrifuged in the cold at 3 000 r.p.m. (2,000 G) for 10 min. and the sediment was dissolved in the original volume of buffer. Later ammonium sulphate to final concentrations of 35 and 50 per cent was added to the supernatant and the centrifuged sediment was treated the same way. In the following these have been termed Fractions I, II and III.

4. Characteristics of the Fractions I, II and III

Inhibitors are partly separated from the other factors of the fibrinolytic system by the euglobulin precipitation. Further separation has been obtained through removal of the activator adsorbed to fibrin from the euglobulin solution, as inhibitors usually are present in serum (Ablondi & De Renzo 1959).

A. Activator activity

Fig. 5 gives dilution curves of the euglobulin fraction in buffer as tested on fibrin standard plates. After removal of the fibrin no fibrinolytic activity was demonstrable in the defibrinated euglobulin solution.

The same figure presents dilution curves for the dissolved fibrin solution and the Fractions I

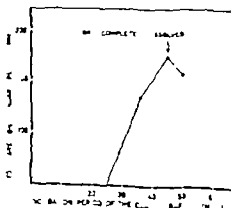


Fig. 4. The appearance of fibrinolytic activity at 37 °C in buffer containing fibrin from the euglobulin fraction of exercise plasma, as tested on standard fibrin plates.

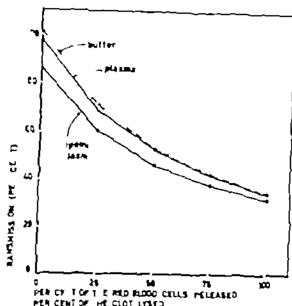


Fig. 2. The reference curves for determination of fibrinolysis in the standard clot systems. The three curves are based on the use of buffer plasma, or lipemic plasma as liquid in the test system. All normal and clear plasmas gave practically identical reference curves. Lipemia, however influenced the colorimetrical determination of hemoglobin. In such cases reference curves had to be drawn for each plasma.

plasma in the liquid is termed the *plasma standard clot system*. The red cells were always compatible with the plasma or serum used in these experiments.

Preparation of the spontaneous activator of plasminogen from plasma after exercise

The purpose of these experiments was to prepare a spontaneous plasminogen activator from blood of normal subjects for the later investigations of clot lysis. Usually blood has only small fibrinolytic activity but the activity increases considerably during exercise.

1. The fibrinolytic activity in plasma and the euglobulin fraction of plasma after exercise

To obtain exercise plasma for the experiments healthy subjects were exposed on different days to slight, medium or hard exercise for three minutes. By hard exercise is meant running up and down a flight of stairs (18 steps of 16 cm each) 28 times (i.e. maximal speed), medium exercise means 22 times and slight exercise 16 times. Blood was collected before and immediately after the exercise and also after one hour of rest in bed. The plasma and the euglobulin fraction were tested on fibrin plates. A considerable rise in activity occurred during the exercise (Fig. 3). The same materials tested on heated plates showed only slight changes, which indicates that the activity on standard plates was mainly due to a plasminogen activator. In the following plasma from blood collected immediately after hard exercise has been used.

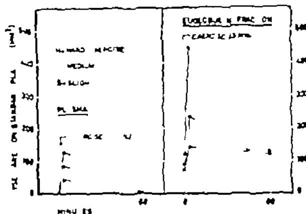
2. Adsorption of the spontaneous activator to fibrin through coagulation

The euglobulin fraction of plasma (after exercise) was clotted at 37 C with one tenth the volume of human thrombin (50 N.I.H. units/ml). The fibrin was rapidly stirred out on a glass rod, washed twice in saline and transferred to a test tube containing a volume of buffer corresponding to half that of the original euglobulin solution. This test tube was incubated at 37 C. The fibrin spontaneously dissolved in the buffer in 30–60 minutes. Fig. 4 shows how the activity was released in the fluid during the incubation period as tested on standard fibrin plates. The fibrinolytic material consisted mainly of activator but plasmin or plasminogen was also present in the solution (Figs. 5 and 6).

3. Fractionation by ammonium sulphate

For the following experiments it was desirable to obtain a still more purified activator. Therefore an attempt was made to separate the act

Fig. 3 The same subject was on different days exposed to three minutes of slight, medium or hard exercise (see text). The figure presents the fibrinolytic activity in plasma and in the corresponding euglobulin fraction of plasma before and immediately after the exercise and after one hour in bed, as tested on standard fibrin plates.



ator from the fibrin split products and the plasmin-plasminogen by means of ammonium sulphate precipitation. The buffer solution was immersed in an ice bath immediately after the complete dissolution of the fibrin. I -cold saturated ammonium sulphate to final concentration of 30 per cent was added. The precipitate was centrifuged in the cold at 3,000 r.p.m. (2,000 G) for 10 min and the sediment was dissolved in the original volume of buffer. Later ammonium sulphate to final concentration of 33 and 50 per cent was added to the supernatant, and the centrifuged sediment was treated the same way. In the following the three have been termed Fractions I, II and III.

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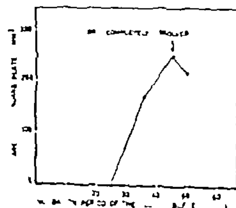


Fig. 4 The appearance of fibrinolytic activity at 37 C in buffer containing fibrin from the euglobulin fraction of exercise plasma, as tested on standard fibrin plates.

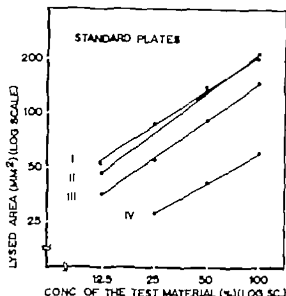


Fig. 5 Fibrinolytic activity in dilution series of various materials as tested on standard fibrin plates (see text).

I Euglobul n solution
II Dissolved fibrin in buffer
III Fraction I (see text)
IV Fraction II (see text)

The fibrin had been dissolved n volume of buffer corresponding to half that of the original euglobulin solut on.

and II as tested on standard fibrin plates. In Fraction III no fibrinolytic activ ty was f und.

B Plasmin and plasminogen

Th total plasmin plasminogen amount was determined as plasmin on heated fibrin plates after activation with rokinase (Blix 1961 II). Fig 6 pictures th decrease of the total plasmin plasminogen content from the euglobulin sol tion to the various Fractions where they are present only in very small amounts.

C Proact vator

Neither the lysed fibrin sol tion no the Fractions I II or III contained measurable amounts of proacti vator e. less than one per cent as compared t the concent tion in plasma

D Proteins

The protein concentration was determined spectrophotometrically at 280 mμ (and correction was made at 320 and 360 mμ)

The protei concentrations in the materials were

In lysed fibrin sol tion	1.8 per mille
In Fraction I	0 5 —»—
In Fraction II	1 0 —»—
In Fraction III	0.2 —»—

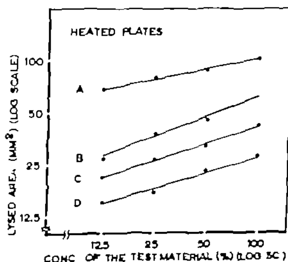


Fig 6 The total plasmin plasm nogen content in various materials, tested as plasmi on heated plates after acti ation w th urokinase

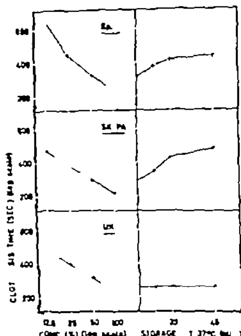
A Euglobulin solution
B Dissol ed fibrin buffe
C Fraction I (see text)
D Fraction II (see text)

Th fibrin had been dissol ed olume of buffer corresponding t half that of the original euglobulin sol tion

Fig 2 Spontaneous activator streptokinase-proactivator or urokinase in dilution series were mixed with fibrinogen and clotted by means of thrombin (see text). The clot lysis times were recorded (left). To the right is shown the lysis times in the same system after incubation of the activators at 37 C.

The 100 per cent concentration in the figures

Spontaneous activator	Undiluted
Streptokinase proactivator	12 5 units per ml
Urokinase	156 units per ml



Plasminogen activators in clot lysis, with special reference to fibrinolytic therapy

In these experiments the same batch of Fraction I as described in the preceding section has been used but in the following this material will be termed the spontaneous activator. Streptokinase proactivator and urokinase have been described under Materials.

1 The effectiveness of activators added to purified fibrinogen before clotting

The spontaneous activator streptokinase proactivator or urokinase was mixed with human fibrinogen and the solution was clotted with thrombin.

The test system

Fibrinogen (50 m)	0 1 ml
Buffer	0 1 ml
Activator solution in dilution series	0.1 ml
Thrombin (10 N I H units per ml)	0 1 ml

The buffer activator and thrombin were taken from an ice bath and added to the fibrinogen at 3 C at 15-second intervals. The clot lysis time from the addition of thrombin was recorded and the results appear in Fig 7

2 The stability of the activators at 37° C

The activators were kept at 37 C and tested at intervals as described for the preceding experiment. The results are given in Fig 7 The urokinase remained stable during the incubation period whereas the spontaneous activator and the streptokinase proactivator gradually became inactivated. The loss of activity was insignificant when the activators were kept at 4 C for two hours.

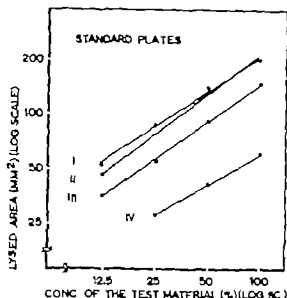


Fig 5 Fibrinolytic act vity in dilution series of arious materials as tested on standard fibrin plates (see text).

I Euglobulin solution

II Dissolved fibrin in buffer

III Fraction I (see text)

IV Fraction II (see text)

The fibrin had been dissol ed in volume of buffer corresponding to half that of the original euglobulin solution

and II as tested on standard fibrin plates. In Fraction III no fibrinolytic activity was found.

B Plasmin and plasminogen

The total plasmin plasminogen amount was determined as plasm n on heated fib n plates after activation w th urokinase (Blix 1961 II). Fig 6 pictures the decrease of the total plasmin-plasminogen content from the euglobul n solu tion to the various Fractions, where they are present only in ery small amounts.

C Proactivator

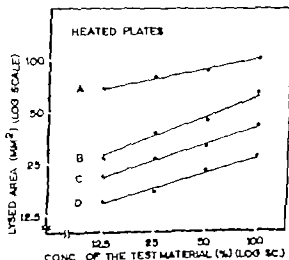
Neither the lysed fibrin solution nor the Frac tions I II or III contained measurable amounts f proact at r less than one per cent compared to the concentr tion in plasma.

D Proteins

The protein concent ation was determined spectrophotometrically at 280 mμ (and correction was made at 320 and 360 mμ)

Th protein concentrations the materials were

In l sed fibrin solution	1.8 per mille
In Fraction I	0 5 —·—
In Fraction II	1 0 —·—
In Fraction III	0.2 —·—



F g 6 The total plasmin plasminogen content in arious materials tested as plasmin on heated plates fter activation with rokinase

A E globulin sol tion

B. Dissol d fibrin in buffer

C. Fraction I (see text)

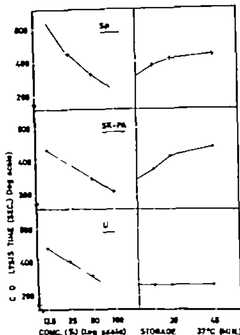
D Fraction II (see text)

The fibrin had been dissol d in olume of b ff correspondi g to half that of the ginal euglobul sol tion

Fig. 7 Spontaneous activator streptokinase-proactivator or urokinase in dilution series ere mixed th fibrinogen and clotted by means of thrombin (see text) The clot lysis times are recorded (lef) T the right is show the lysis times in the same system after incubation of the activators at 37 C.

The 100 per cent concentration in the figures

Spontaneous activator	Undiluted
Streptokinase-proactivator	12 5 units per ml
Urokinase	156 units per ml



Plasminogen activators in clot lysis, with special reference to fibrinolytic therapy

In these experiments the same batch of Fraction I as described in the preceding section has been used but in the following this material will be termed the spontaneous acti ator Streptokinase-proactivator and urokinase have been described under Materials.

1 The effectiveness of activators added to purified fibrinogen befor lotting

The spontaneous activ tor streptokinase proactivator or urokinase was mixed with human fibrinogen and the sol tion was clotted with thrombin.

The test system

Fibrinogen (50 mg)	0.1 ml
Buffer	0 1 ml
Activator solution in dilution series	0 1 ml
Thrombin (10 N I H units per ml)	0 1 ml

The buffer activator and thrombin were taken from an ice bath and dded to the fibrinogen at 37° C t 15-second intervals. The clot lysis time from the addition of thrombin was recorded and the results appear in Fig 7

2 The stability of the activators at 37° C

The activators were kept at 37° C and tested at intervals as described for the preceding experiment. The results are given in Fig. 7 The urokinase remained stable during the incubation period whereas the spontaneous acti ator and the streptokinase-proactivator gradually became inactivated. The loss of activity was insignificant when the activators were kept at 4 C for two hours.

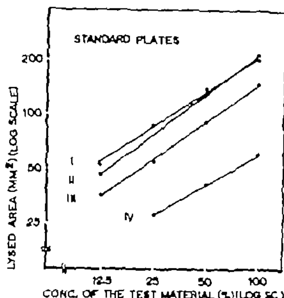


Fig. 5 Fibrinolytic activity in dilution series of various materials, as tested on standard fibrin plates (see text).

I Euglobulin solution
II Dissolved fibrin in buffer
III Fraction I (see text)
IV Fraction II (see text)

The fibrin had been dissolved in a volume of buffer corresponding to half that of the original euglobulin solution

and *II* as tested on standard fibrin plates. In Fraction III *no fibrinolytic activity* was found.

B Plasmin and plasminogen

The total plasmin plasminogen amount was determined as plasmin on heated fibrin plates after activation with urokinase (Blix 1961 II). Fig 6 pictures the decrease of the total plasmin plasminogen content from the euglobulin solution to the various Fractions where they are present only in very small amounts.

C *Proactivator*

Neither the lysed fibrin solution nor the Fractions I II or III contained measurable amounts of proactivator less than one per cent as compared to the concentration in plasma.

D *Proteins*

The protein concentration was determined spectrophotometrically at 280 mμ (and correction was made at *320 and 360 mμ*).

The protein concentrations in the materials were

In lysed fibrin solution	1 8 per mille
In Fraction I	*0.5* ——
In Fraction II	1 0 ——
In Fraction III	0 2 ——

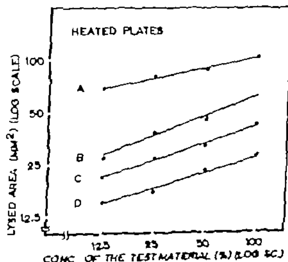


Fig. 6 The total plasmin-plasminogen content in various material tested as plasmin on heated plates after activation with urokinase

A. Euglobulin solution
B. Dissolved fibrin in buffer
C. Fraction *I* (see text)
D Fraction II (see text)

The fibrin *had been dissolved* in a volume of buffer corresponding to half that of the original *euglobulin solution.*

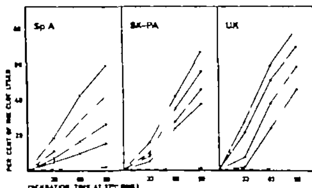


Fig. 9 Spontaneous activator streptokinase-proactivator and urokinase in dilution series were tested in the purified standard clot system. The curves illustrate the progress of the clot lysis.

The activators were tested undiluted (curve 1), diluted / (2), / (3) and / (4). The dotted lines (curve 5) show the control clots, which were only exposed to buffer.

The curves labelled 1 correspond to spontaneous activator undiluted, streptokinase-proactivator 25 units per ml and urokinase 312 units per ml of liquid.

B. Fibrin derived from plasma

Plasma was mixed with activator solutions of approximately the same activity at room temperature and thrombin was added five seconds later. The fibrin was carefully stirred out onto a glass rod and removed. The activator solutions were tested as described above before thrombin was added (Solution 1) and immediately after the defibrination (Solution 2).

The experiment procedure

Solution 1	Plasma	0.2 ml
	Activator	0.2 ml
	Buffer	0.2 ml

Solution 2	Plasma	0.2 ml
	Activator	0.2 ml
	Thrombin (10 NIH units/ml)	0.2 ml

Removal of fibrin.

The results appear in Fig. 8. Neither was fibrinolytic activity demonstrable in serum from normal individuals after exercise. The results are in agreement with the preceding experiments. Spontaneous activator and streptokinase-proactivator are adsorbed to fibrin through coagulation, while urokinase is not.

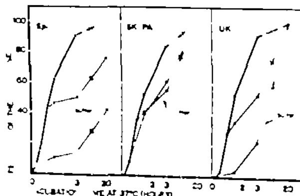


Fig. 10 The purified standard clot system.

The figure shows the progress of the clot lysis with activators in the liquid (thick line), and when clots are removed after 10 or 60 min, carefully washed in saline and transferred to plastic tubes which contain buffer only (thin lines).

The concentrations in the original liquid:

Spontaneous activator diluted 50 per cent

Streptokinase-proactivator 12.5 units per ml

Urokinase 40 units per ml.

3 Adsorption of activators to fibrin through coagulation

A Fibrin derived from purified fibrinogen

Human fibrinogen was mixed with activator solutions of approximately the same activity at room temperature and after five seconds thrombin was added. The fibrin was removed by stirring with a glass rod The activator solutions were tested as described above before fibrinogen was added (Solution A) and immediately after the defibrination (Solution B)

The experiment procedure

Solution A	Activator	0 2 ml
	Buffer	0.2 ml
	Buffer	0 1 ml
Solution B	Activator	0 2 ml
	Fibrinogen (100 mg %)	0.2 ml
	Thrombin (10 N I H units per ml)	0 1 ml

Removal of fibrin

The results are reported in Table II It is indicated that the spontaneous activator and the streptokinase proactivator are strongly adsorbed to fibrin while urokinase is not. The spontaneous activator could be released from the fibrin (page 7) and other experiments showed the same for streptokinase proactivator The shorter lysis time in urokinase solution after the defibrination is probably due to contamination of fibrinogen and thrombin with plasminogen (see Materials) which is not completely adsorbed (see Discussion).

Table II The fibrinolytic activity of spontaneous activator streptokinase-proactivator or urokinase (solutions A) were tested in a clot lysis system (see text) The same activators were mixed with fibrinogen and the fibrin quickly removed after clotting with thrombin. The defibrinated solutions (B) were tested in the same system.

Test material	Clot lysis time (sec.)	
	Solution A	Solution B
Spontaneous activator	370	1 600
Streptokinase-proactivator	320	1,200
Urokinase	320	252

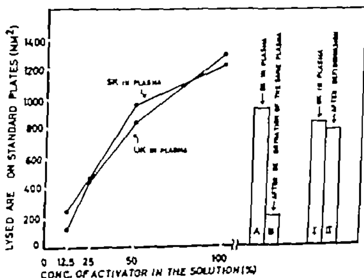


Fig 8. The curves present the fibrinolytic activity in 0 2 ml plasma mixed with 0 2 ml of dilution series of streptokinase and urokinase as tested on standard fibrin plates. 100 per cent activities were for streptokinase 250 units and for urokinase 156 units per ml of buffer

To the right is shown the activity in plasma mixed with streptokinase (A) and the activity in the same plasma after defibrination and removal of fibrin (B)

The other columns give the same experiment but with urokinase (I and II). Adsorption of urokinase to fibrin is insignificant.

proactivator but considerable also in those primarily exposed to urokinase although urokinase in the previous experiments was not adsorbed to fibrin and less marked for the spontaneous activator Therefore this clot lysis is not explainable only by adsorption of the fibrinolytic agents diffusion into the clot might also play a role in the continued lysis a phenomenon however which in the corresponding plasma clot system was of no practical importance (see below p 20).

5 I fluence of serum on the ate of the clot lysis in the purified clot system

In the following experiments the effectiveness of only streptokinase-proactivator and of urokinase was tested as the investigations were made with a special iew to the possible use of activators in fibrinolytic therapy Unless otherwise stated plasma with relatively low streptokinase antibody concentration was used.

Of the buffer liquid 75 per cent (2.1 ml) was replaced by undiluted serum or serum diluted t / and The activators were dissolved in the remaining 0 7 ml of buffer liquid. The influence of these serum concentrations on the clot lysis is shown in Fig. 11 The undiluted serum is seen to inhib t the clot lysis while weak serum concentrations in the liq id would increase the rate of the lysis.

In the next experiment 75 per cent of the liqu d was replaced by serum from six normal blood donors of the same blood group (0) The results (Fig 12) reflect the great variation n the inhibitory effect of streptokinase-proactivator and the absence of marked ariation in the clot lysis where urokinase was th activ agent.

It appears from Fig 12 (left) that three of the sera caused almost complete inhibition of the clot lysis. By an immunological technique (see Methods) streptokinase antibodies were clearly demonstrable in these three sera, but not in the other ones.

6 Influence of anticoagulants fat and platelets in plasma on the rate f clot lysis in the plasma standard clot system

A It has been known for long time that anticoagulants in plasma may interfere with fibrinolysis. In order to assist in the choice of anticoagulant f r the plasma clot system a supplementary study was perf rmed.

Plasma was collected in citrate oxalate and heparin (25 units per ml of saline). The standard clot lysis in these plasma specimens was compared to those in saline serum and citrated serum (see Methods collection of blood). In the following the term units of activators per ml of plasma will signify units per ml of plasma including the anticoagulant. The standard clots n this experiment were prepared from citrated plasma.

Table III Blood from the same donor was collected in arious anticoagulants (see M thods, collection of blood) Standard clot were prepared from the citrated plasma. Urokinase (208 unit per ml plasma) was used as activator in the arious plasmas and sera

Anticoagulant	Per cent of the standard lot lysed		
	20 min.	60 min	120min.
Citrate (3 13 gm)	12	38	66
Oxalate (2.5 gm)	10	32	56
Heparin (25 ml)	8	17	24
Saline serum	6	31	60
Citrate serum	11	42	72

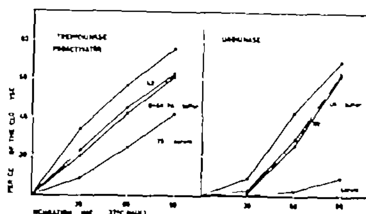


Fig 11 The influence on clot lysis of various concentrations of serum added to the liquid in the purified standard clot system. The curve labelled 0 shows the rate of lysis without serum in the system. The other curves show the rate of lysis when 75 per cent (2.1 ml) of the fluid was substituted with serum, undiluted, diluted to 1/4 and to 1/16 in buffer

Activator concentrations in all the liquids

Streptokinase proactivator 12.5 units per ml

Urokinase 40 units per ml

4 The effect of activators on the surface of purified fibrin clots

The spontaneous activator streptokinase-proactivator or urokinase in four dilutions were tested in the purified standard clot system as previously described (page 4) The results are given in Fig 9

For the following experiments the three activators were used in concentrations which produced approximately the same per cent of lysis of the standard clot in the course of three hours. After 10 or 60 min. the clots were removed carefully washed in saline and transferred to other plastic tubes containing the same buffer volume as the liquid (the activator solution) in the original tubes. The continued lysis of the clots were observed and the results are given in Fig 10 It is seen that the clot lysis went on slowly even after the removal of the clot from the activator milieu This was most marked in the clots primarily exposed to streptokinase

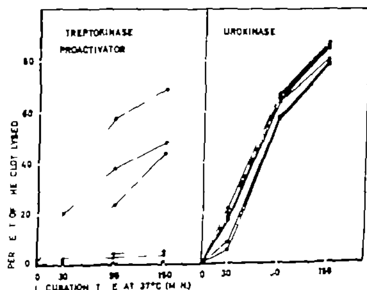


Fig 12 The influence on the clot lysis of six sera from normal blood donors added to the liquid in the purified standard clot system 75 per cent of the liquid (2 1 ml) was substituted with serum The clot lysis was recorded

Activator concentrations in the final liquid

Streptokinase-proactivator 25 units per ml

Urokinase 80 units per ml.

proactivator but considerable also in those primarily exposed to urokinase although urokinase in the previous ex periments was not adsorbed to fibrin and less marked for the spontaneous activator Therefore this clot lysis is not explain able only by adsorption of the fibrino- lytic agents diffusion into the clot might also play a role in the continued lysis a *phenomenon however which in the cor* responding plasma clot system was of no practical importance (see below p 20)

5 Influence of serum on the rate of the clot lysis in the purified clot system

In the following experiments the effec tiveness of only streptokinase-proacti vator and of urokinase was tested, as the investigations were made with a special view to the possible use of activators in fibrinolytic therapy Unless otherwise stated plasma with relatively low strepto- kinase antibody concentration was used.

Of the buffer liquid 75 per cent (2.1 ml) was replaced by undiluted serum or serum diluted to and The acti vators were dissolved in the remaining 0 7 ml of buffer liquid. The influence of these serum concentrations on the clot lysis is shown in Fig 11 The undiluted serum is seen to inhibit the clot lysis while weak serum concentrations in the liquid would increase the rate of the lysis.

In the next experiment 75 per cent of the liq id was replaced by serum from six normal blood donors of the same blood group (0) The results (Fig 12) reflect the great ariation in the nhibi tory effect of streptokinase proactivator and the absence of marked variation in the clot lysis where urokinase was the activ gent.

It appears from Fig 12 (left) that three of the sera caused almost complete inhi- bition of the clot lysis. By an immuno- logical technique (see Methods) strepto- kinase antibodies were clearly demon strable in these three sera but not in the other ones.

6 Influence of anticoagulants fat and platelets in plasma on the rate of clot lysis in the plasma standard clot system

A. It has been known for long time that anticoagulants in plasma may inter fere with fibrinolysis. In order to assist in the choice of anticoagulant for the plasma clot system a supplementary study was performed.

Plasma was collected in citrate oxalate and heparin (25 units per ml of saline) The standard clot lysis in these plasma specimens was compared to those n saline serum and citrated serum (see Methods collection of blood). In the following th term units of activators per ml of plasma will signify units per ml of plasma including the anticoagulant. The standard clots in this experiment were *prepared from citrated plasma.*

Table III Blood from the same donor was collected in various anticoagulants (see 31 Methods, collection of blood) Standard clots were prepared from the citrated plasma. Urokinase (03 units per ml plasma) was used as activator in the various plasmas and sera

Anticoagulant	Per cent of the standard clot lysed		
	20 min.	60 min.	120min.
Citrate (3.13 gm)	12	38	66
Oxalate (2.5 gm)	10	32	56
Heparin (25 u/ml)	8	17	24
Saline serum	6	31	60
Citrate serum	11	42	72

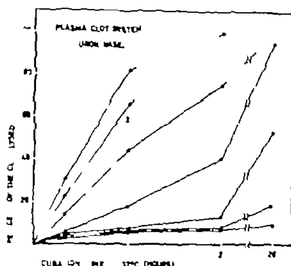


Fig 13 Streptokinase in various concentrations (0 7 ml) was added to 2.1 ml oxalated plasma, and the lysis of oxalated plasma standard clots in these liquids was recorded.

The calculated concentrations of streptokinase per ml of liquid in the system

1 2,000 units per ml of plasma
2 500
3 200 „ „
4 50
5 20 „
6 10 „ „
7 0

(With citrated plasma the results were practically identical the clot lysis was slightly more pronounced)

Increase in the rate of the clot lysis with higher streptokinase concentrations was insignificant. At 12,000 units per ml of plasma slight partial inhibition of the clot lysis was observed.

The results are given in Table III They show agreement with an earlier experiment (Blix 1961) The most remarkable finding was the inhibition by heparin. Another supplementary study revealed that even within the range of therapeutical heparin doses (1–3 units per ml of plasma) there will be a slight inhibitory effect on the clot lysis by urokinase The inhibitory effect on streptokinase was less pronounced

In the following experiments citrated or oxalated plasma was used in the standard clot and in the liquid

B No difference in the rate of the clot lyses was observed whether lipemic plasma was used in the liquid or for preparation of the clots or not.

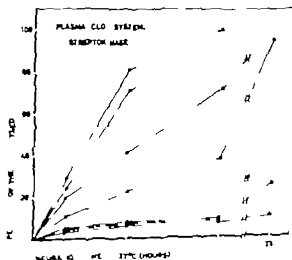


Fig 14 Urokinase in various concentrations (0 7 ml) was added to 2 1 ml oxalated plasma and the lysis of oxalated plasma standard clots in these liquids was recorded

The calculated concentrations of urokinase per ml of plasma in the liquid

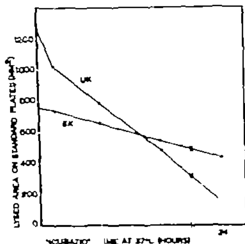
1 832 units per ml of plasma
2 416
3 208
4 104
5 52
6 26
7 0

(With citrated plasma the results were practically identical the clot lysis was slightly more pronounced).

Fig. 15 Samples taken at intervals from the rotating plastic tubes – hich contained 2.1 ml oxalated plasma and 0.7 ml streptokinase or urokinase – were ated on standard fibrin plates.

The activator concentrations

Streptokinase 100 units per ml plasma
Urokinase 104



C. No difference in the rate of the clot lysis was demonstrable whether platelet poor (15,000 per c.mm) or platelet rich plasma (350,000 per c.mm) was used in the liquid. A slight inconstant clot retraction was observed however in the platelet rich liquid and the clot also had a tendency to adhere to the wall. Platelet rich red cell suspension in the clot induced retraction and made observations unreliable.

7 The effect of activators in the plasma standard clot system

A. Streptokinase and urokinase in various concentrations were tested in the system as shown and described in Figs. 13 and 14

B. In order t study the fibrinolytic activity in plasma containing activators during the incubation at 37°C 2.1 ml of plasma was mixed with 0 7 ml of activators in the plastic tubes and placed on the automatic record player At intervals small samples were removed and tested

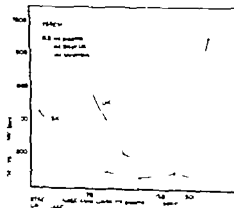


Fig 16 Oxalated plasma was mixed with streptokinase or urokinase and clotted ith thrombin (see he text) The clot lysis ime as recorded (NB! The streptokinase and urokinase units are not defined the same way)

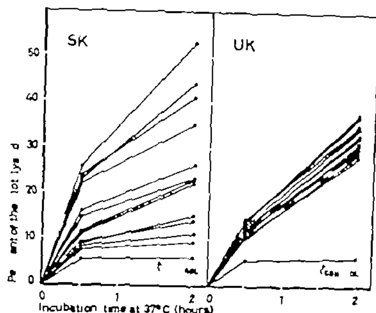


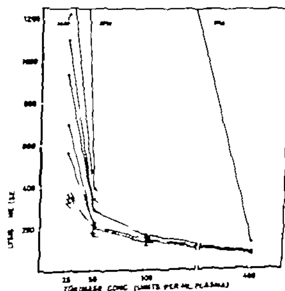
Fig 17 The plasma standard clot system. Strept kinase (100 units per ml plasma left) and rokinase (104 units per ml plasma right) were tested in liquids containing citrated plasma from 12 normal subjects. The standard clots wer prepared from one sample of citrated plasma.

on standard fibrin plates (Fig 15) The results differed from the observations of the pure activator solutions (Fig 7) in that the urokinase activity disappeared more quickly than the streptokinase proactivator activity

C For comparison of the intra clot lysis with the surface clot lysis acti vators in various concentrations were mixed with plasma before the clotting with *thrombin and the lysis times re* corded. The system was

Oxalated plasma	0.2 ml
Activator (see Fig 18)	0.2 ml
Thrombin (20 N I H units per ml)	*0.2 ml*

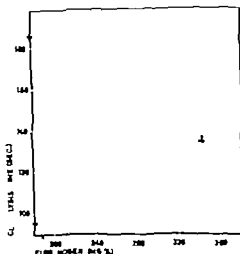
The materials were kept in ice water and added to the plasma at 37 C at inter vals of 15 sec. The clot lysis time from the addition of thrombin was recorded.



F g 18 C trated plasma from 12 normal subject was mixed w th ous concentrations of trepto-kinase and clotted with thromb (se ext) The clot lysis t mes w recorded

If d awn on double logari hmic paper more straightlined curves were obtained.

Fig. 19 Relation between fibrinogen concentration in the twel plasmas and the intra clot lysis time (see text) of the same plasmas after mixing with activators and clotting by thrombin.
The concentration of activators
Streptokinase 100 units per ml plasma (black circles)
Urokinase 1,000 (open circles)



The results are given in Fig 16. No inhibition of clot lysis with increased concentration of urokinase was recorded. It also appears that streptokinase was more effective than urokinase in intra clot lysis if concentrations were used which would give approximately the same rate of clot lysis in the plasma standard clot system (Figs. 13 and 14).

The same plasma was used for the experiments A B and C

8 *The effect of activators in twelve normal plasmas*

A. Citrated plasmas from 12 normal subjects mixed with activators were used as liquids in the plasma standard clot system. The clots were prepared from one plasma with a low anti-streptokinase level and a fibrinogen concentration of 265 mg %.

The results are presented in Fig 17 and they show again the great individual variation in the inhibitory effect on streptokinase.

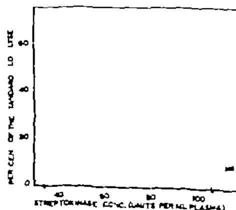


Fig 20 Citrated plasma from the 12 normal subjects compared in the intra clot lysis system and the surface standard plasma clot system. The abscissa show the concentration of streptokinase necessary in plasma to give an intra clot lysis time of 200 seconds, and the ordinate show the per cent of the standard clot lysed in the course of two hours by means of 100 units of streptokinase per ml plasma as the liquid.

Table IV Plasmas from 12 normal subjects were mixed with urokinase in four concentrations and clotted by thrombin (see text). The clot lysis times were recorded

Subject	CLOT LYSIS TIME (SEC.)			
	Urokinase (units per ml plasma)			
	4 000	1 000	250	62.5
1	65	121	276	1020
2	65	177	298	1255
3	66	126	307	1350
4	73	136	305	1240
5	63	124	288	1140
6	6	127	290	1105
7	78	138	356	1530
8	66	118	285	1055
9	73	139	327	1450
10	68	134	301	1070
11	67	131	308	1245
12	65	124	287	1050

A patient with an extraordinarily high concentration of anti streptokinase in plasma has previously been described (Blix 1961 I). In this plasma it was possible to obtain only insignificant lysis of the standard clot even with concentrations of streptokinase as high as 2,500 units per ml which was found to be the optimal concentration for intra clot lysis in this plasma.

The urokinase induced fibrinolysis is much more uniform indicating that the individual variation in urokinase and plasmin inhibitors is of less importance.

B The effect of activators in the intra clot lysis was tested in order to see if this kind of fibrinolysis could be correlated to the surface clot lysis in the standard system. The system was the same as that described above.

The results are given in Fig 18 and Table IV. Here too the spreading of values obtained with streptokinase is obvious while the spreading of values obtained with urokinase was insignificant. No correlation between the fibrinogen concentration of the plasmas (range 203–344 mg %, mean 273 mg %) and the intra clot lysis times could be revealed (Fig 19).

C The concentration of streptokinase which in each plasma would give an intra clot lysis time of 200 seconds was

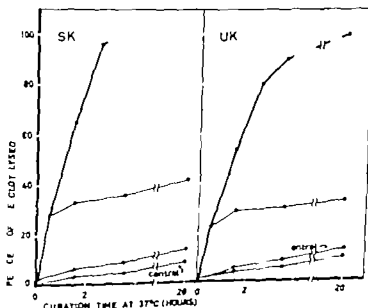


Fig 21 Th plasma standard clot system

The figur show the l ss of the oxalated plasma clot w th acti tors the oxalated plasma liquid (thick line) and how the l is ceases when the clots ar remo d (fu 5 or 30 min ca f ll washed in saline and t ansf red t plastic tubes w th the same plasma liquid w thout act tors (th l nes)

The ontrol is lot from the same y t m w th no act at rs from the beginn g

The act tor concentrations
Streptokinase
200 nit per ml of plasma
Urokinase
208 units pe ml of plasma

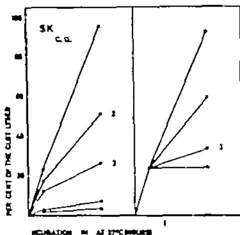
Fig 22. The plasma standard clot system.

The liquid consisted of 2.1 ml citrated plasma and 0.49 ml of streptokinase in buffer 0.21 ml of epsilon-amino-caproic acid in dilution series in buffer was added immediately (left) or 30 min. after the clot (right).

The streptokinase concentration in the liquid as 300 units per ml of plasma.

The final concentration of epsilon-amino-caproic acid in plasma (/)

1 0.0 per cent
2. 0.02 per cent
3. 0.08 per cent
4 0.32 per cent
5 Control Standard clot in liquid without streptokinase and psilon-amino-caproic acid.



read from the almost straight curves obtained on a double logarithmic paper (see Fig 18). These values were in each case correlated to the per cent of the standard clot lysed in two hours by means of 100 units of streptokinase per ml plasma as seen in Fig 17 The results are gi en in Fig 20. They show a fairly good correlation indicating that it is possible to draw lim ted conclusions from the intra clot lysis times as to what may be obtained in the surface clot lysis

D With an improved technique fur ther immunological studies concerning the streptokinase antibody titer in the twelve plasmas are in progress and will be reported later (Remakou 1962). The preliminary results roughly show an in verse proportion between the effective-ness of streptokinase acti ated plasmas in the standard clot system and their anti body levels.

Fig 23 The plasma standard clot system.

The liquid consisted of 2 1 ml citrated plasma and 0 49 ml of urokinase in buffer 0.21 ml of epsilon-amino-caproic acid in dilution series in buffer as added immediately (lef) or 30 min. after the clot (right). The urokinase concentration in the liquid as 104 units per ml of plasma.

The final epsilon-amino-caproic acid concentration in plasma (w/v)

1 0.0 per cent
2 0.005 per cent
3 0.02 per cent
4 0.08 per cent
5 Control Standard clot in liquid ithout urokinase and epsilon-amino-caproic acid

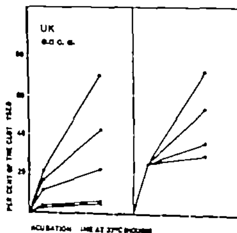


Table IV Plasmas from 1 normal subjects mixed with urokinase four concentrations and clotted by thrombin (see text) The clot lysis times were recorded

Subject No	CLOT LYSIS TIME (SEC.)			
	Urokinase (units per ml plasma)			
	4 000	1 000	250	62.5
1	65	121	276	1020
2	65	1 7	298	1255
3	66	126	307	1350
4	73	136	305	1240
5	63	124	288	1140
6	65	127	290	1105
7	78	138	356	1530
8	66	118	285	1055
9	73	139	327	1450
10	68	134	301	1070
11	67	131	308	1245
12	65	124	287	1050

A patient with an extraordinarily high concentration of anti streptokinase in plasma has previously been described (Blix 1961 I) In this plasma it was possible to obtain only insignificant lysis of the standard clot even with concentrations of streptokinase as high as 2,500 units per ml which was found to be the optimal concentration for intra clot lysis in this plasma.

The urokinase induced fibrinolysis is much more uniform indicating that the individual variation in urokinase and plasmin inhibitors is of less importance.

B The effect of activators in the intra clot lysis was tested in order to see if this kind of fibrinolysis could be correlated to the surface clot lysis in the standard system. The system was the same as that described above.

The results are given in Fig 18 and Table IV Here too the spreading of values obtained with streptokinase is obvious while the spreading of values obtained with urokinase was insignificant. No correlation between the fibrinogen concentration of the plasmas (range 203–344 mg % mean 273 mg %) and the *intra clot lysis times could be revealed* (Fig 19)

C The concentration of streptokinase which in each plasma would give an intra clot lysis time of 200 seconds was

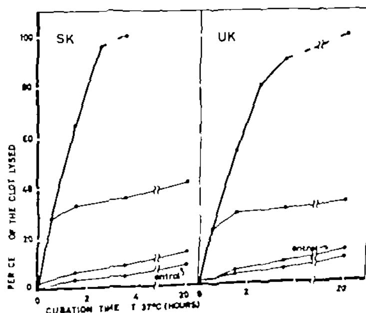


Fig 21 The plasma standard clot system

The figure shows the lysis of the oxalated plasma clots with activators in the oxalated plasma liquid (thick line) and how the lysis ceases when the clots are removed after 5 or 30 min carefully washed in saline and transferred to plastic tubes with the same plasma liquid without activators (thin lines)

The control is a clot from the same system with no activators from the beginning

The activator concentrations

Streptokinase

200 units per ml of plasma

Urokinase

203 units per ml of plasma

tional separation from plasmin-plasminogen – and to a lesser degree from the fibrin split products – has been obtained. The final product once more adsorbable to fibrin during coagulation has been used in comparative studies with activators recommended for thrombolytic therapy

2 Adsorption of streptokinase-proactivator and urokinase to fibrin

Müllertz (1956) and Lassen (1958 II) reported that when added to plasma or fibrinogen before clotting, the streptokinase induced activator was strongly adsorbed to fibrin. The finding has been confirmed by us but no adsorption of urokinase has been obtained during coagulation.

3 Activators in fibrinolytic therapy

When testing the effectiveness of fibrinolytic agents on preformed I[131] labelled clots *in vitro* Alkjaersig *et al.* (1959) found activators more active clot lysing agents than plasmin. They believe that this fibrinolytic process occurs as a result of activation of plasminogen in the thrombus. Their finding has been confirmed by *in vivo* dissolution of experimentally induced thrombi in peripheral veins of human volunteers (Johnson & McCarty 1959 and 1961).

Streptokinase was first tried intravenously in animal experiments in 1952 (Johnson and Tillett). Since 1955 (Tillett *et al.*) intravenous injections of streptokinase have been given to patients and repeatedly tried in thrombolytic therapy. No convincing controlled studies have been reported however. Urokinase – the plasminogen activator from human urine – has recently been intravenously administered to dogs and human individuals without major side effects (From Hansen *et al.* 1961)

4 Problems related to fibrinolytic therapy

So far there is no general agreement about the optimal intensity and duration of the treatment (Colloquium on effects and side effects of fibrinolytic therapy 8th Congress of the European Society of Haematology Wien 1961).

If the adsorption of an activator to fibrin could also cause selective concentration on the surface of thrombi this would be of great importance to the effectiveness of thrombolytic therapy. A simple and rapid method has been worked out for study of the effectiveness and the adsorption mechanism of the activators on the fibrin surface. Similar methods have previously been reported. In 1959 v Kaulla presented a method where the decrease in volume of a preformed clot in the stem of a protein sedimentation tube could be directly measured. However a rather long incubation period for the registration of clot lysis seemed necessary. The same year Alkjaersig *et al.* described their quantitation of fibrinolysis by the use of I[131] labelled human plasma clots a method which requires equipment not available in most laboratories. In 1961 Fischbacher utilized the thrombelastograph for the same purpose.

Several objections may be raised against experiments using preformed standard clots. Thus the fibrin split products are not removed from the closed system the

9 Lack of effective adsorption of activators to the surface of plasma standard clots

For this experiment streptokinase and urokinase were used in concentrations which would lyse approximately the same per cent of the standard plasma clots in the course of three hours. After 5 or 30 min. the clots were removed carefully washed in saline and transferred to other plastic tubes containing the same volume of plasma and buffer as that of plasma and activators in buffer in the original tubes. The continued lysis of the clots in these tubes was observed and the results are given in Fig 21 The clot lysis ceased as the clots were removed from the active plasma. The experiment was reproduced with citrated plasma in clots and liquid and also with thrombin as the clotting agent for preparation of the standard clots.

10 The inhibitory effect of epsilon-amino-caproic acid on the clot lysis

A. Inhibitory effect on streptokinase-proactivator

Epsilon amino-caproic acid in various amounts was added to the plasma before the introduction of streptokinase. Epsilon amino-caproic acid in 0 3 per cent concentration in the plasma completely inhibited the clot lysis. If epsilon amino-caproic acid was added after half an hour to the tube which contained plasma streptokinase and the standard clot the very same inhibition occurred. The results are given in Fig 22.

B Inhibitory effect on urokinase

The same results were observed as for streptokinase except that only 0 08 per cent of epsilon amino-caproic acid was needed in the plasma to produce complete inhibition of the clot lysis. The results appear in Fig 23

Discussion

1 Adsorption of the fibrinolytic components to fibrin during coagulation

In 1908 Barker reported the presence of a proteolytic enzyme in fibrin. Later several investigators have called attention to the adsorption of fibrinolytic components to fibrin The mechanism is believed to be of great physiological importance (Astrup 1956). Of the available plasminogen in plasma about 30 per cent is adsorbed to fibrin during clot formation (Sawyer *et al* 1961). There is a close relationship between plasminogen and proactivator (Alkjaersig *et al* 1959) In our experiments we have recently found that about 35 per cent of proactivator is adsorbed to fibrin from plasma (Blix 1962) Macfarlane and Pilling (1947 cit Macfarlane & Biggs 1948) found that the fibrinolytic material from the euglobulin fraction of plasma could be adsorbed to fibrin and released into saline during clot lysis. Their results have not been published however Biggs *et al* (1947) observed a considerable increase in the fibrinolytic activity in plasma during exercise According to Sherry *et al* (1959) the underlying mechanism involved the appearance in the blood of a plasminogen activator The present study proves that this spontaneous activator is capable of being strongly adsorbed to fibrin during coagulation. This quality we have utilized in the preparation of this activator By ammonium sulphate precipitation addi

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artificial prepared clots and the use of anticoagulants in plasma may make comparison with *in vivo* conditions doubtful. The results and conclusions must therefore be considered with caution

The results obtained with the present standard clot system indicate that the selective adsorption to fibrin surfaces is inconsiderable and of no practical importance to the fibrinolytic therapy. Even from a liquid which contained plasma with high streptokinase proactivator concentration the preformed clots were unable to adsorb sufficient amounts of activator for continued lysis in an activator free plasma liquid. This finding agrees with an earlier report by Fletcher *et al* (1958) who found the uptake of labelled streptokinase on preformed clots to be negligible.

The present investigation indicates that for a successful thrombolysis a high activator concentration in plasma must be maintained. Fat and platelets in plasma did not influence the clot lysis

The effectiveness of urokinase in various plasmas on the preformed clots was much more constant than that of streptokinase. The possibility of a more standardized treatment with this activator therefore seems indicated. Doses which in our system would give distinct lysis of the preformed clots within a few hours have been given intravenously in single injections without major complications (From Hansen *et al* 1961)

Concerning streptokinase therapy however the considerable variation in streptokinase antibodies necessitates an individual dose prediction test a point which already has been emphasized by several investigators (Johnson *et al* 1957 Fletcher *et al* 1959 I Fischbacher 1960 Olow & Nilsson 1961). When increasing the streptokinase amount in plasma before the clotting by thrombin the lysis time will rapidly shorten until a certain streptokinase concentration has been reached. Then the lysis time will remain nearly constant over a wide range. At very high concentrations the lysis time will again increase (Christensen 1949). The usual dose prediction tests recommended have been mixing the patient's blood or plasma with streptokinase in dilution series and recording the clot lysis times. Consequently the substrate in all these tests has been the fibrin derived from the plasma fibrinogen which shows considerable individual variations. However we were not able to demonstrate correlation between clot lysis times and fibrinogen values in the twelve normal plasmas. On the other hand we have found a relatively good relationship between the intra clot lysis time and the effect of the activated plasmas on the preformed standard clots. Therefore it seems possible to draw limited conclusions from the simple dose prediction test to the effect of streptokinase on preformed fibrin in a certain plasma. Supplementary studies regarding the streptokinase antibodies using an improved immunological technique are in progress (Reinskou 1962). The present investigation suggests that the plasma concentrations of streptokinase used in thrombolytic therapy should probably be kept within the wide optimal range in intra clot lysis in our system this was attained when giving a lysis time of less than 200 seconds.

Streptokinase in doses roughly corres

ponding to these concentrations has been administered to patients, though by means of infusions over a period of 1 to 2 hours without severe complications (Olow & Nilsson 1961). Much attention has been paid to the practical use of streptokinase (Johnson & Tillett 1952 Tillett *et al.* 1955 Fletcher *et al.* 1958 Fletcher *et al.* 1959 I and II Olow & Nilsson 1961 Deutsch & Fischer 1961). The intensity of the maintenance therapy depends on the clearance rate of activators from the blood, and on the possible *transient neutralization of* antibodies by the initial dose of streptokinase. These problems can only be studied *in vivo* and will not be dealt with here.

5 The effect of epsilon-amino-caproic acid on the lysis of preformed clots

Ablondi & De Renzo (1959) with their preformed I^{131} labelled fibrin clots found little inhibition of clot lysis in the presence of epsilon-amino-caproic acid although plasminogen activation was completely *inhibited* in the surrounding plasma. The system was extremely artificial however because the clots contained large amounts of plasminogen. By the use of clots not fortified by plasminogen partial inhibition of the lysis occurred. It has been suggested that by simultaneous administration of epsilon-amino-caproic acid and streptokinase the side effects due to hyperplasminemia might possibly be avoided without counteracting the thrombolysis (Nilsson *et al* 1961 Olow & Nilsson 1961). Our examinations in agreement with those performed by Alkjaersig *et al.* (1959) with labelled clots do not support this view. Administered together with activators or after the clot lysis *had* commenced epsilon-amino-caproic acid in concentrations recommended for therapy strongly inhibited lysis of the standard clots.

Summary

1 The spontaneous activator in plasma after exercise is completely adsorbed to fibrin through coagulation of the euglobulin fraction. A method for partial separation of the activator from other plasma proteins has been described.

2. Streptokinase-proactivator as well as readily adsorbed to fibrin during coagulation while urokinase is not.

3 The effectiveness of spontaneous activator streptokinase-proactivator and urokinase in clot lysis has been compared. For investigation of the effect of the agents on fibrin surface a new simple and reliable preformed standard clot system has been worked out. Quantitative determination of the clot lysis is obtained through determination of hemoglobin in red cells released from the clot.

4 The adsorption of activators to the preformed clots is insignificant. Therefore in thrombolytic therapy it will hardly be possible to make practical use of the selective adsorption to fibrin which is found when streptokinase-proactivator is present before coagulation. In such treatment urokinase seems as good as streptokinase and with markedly smaller variation in effect from one subject to another The importance of the streptokinase antibodies and the usual dose prediction test in plasma has been evaluated.

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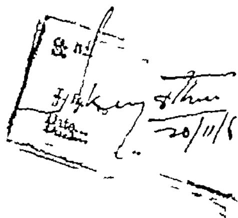
ACTA MEDICA SCANDINAVICA

SUPPLEMENTUM 385

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BY

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DEPARTMENT OF RADIOTHERAPY (HEAD: PROF. S. MUSTAKALLIO),
AND DEPARTMENT OF NEUROSURGERY, UNIVERSITY CENTRAL HOSPITAL, HELSINKI,
MEDICAL DEPARTMENT, DEACONESS HOSPITAL, HELSINKI

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INTRODUCTION

The endocrine treatment of mammary cancer was much stimulated by the introduction of ablative surgery in the form of hypophysectomy (LUFT OLIVECRONA & SJÖGREN 1952) and adrenalectomy (HUGGINS & BERGENSTAL 1952). The former method, at least, seems to have acquired a permanent place in the treatment of metastasizing breast cancer. The significance of oestrogenic hormones as a basis for the endocrine treatment of mammary cancer and for the concept of hormone dependence of certain cancer cases has apparently been overestimated. Thus, after castration or hypophysectomy no significant correlation has been demonstrated between a favourable clinical response and a decrease in the excretion of oestrogenic hormones in the urine or in the biological oestrogenic effect on the vaginal mucous membranes (STRONG *et al.* 1956, BULBROOK *et al.* 1958, GORDON & SEGALOFF 1958, SCOWEN 1958, HUIS BRUMMER *et al.* 1960, MCALLISTER *et al.* 1960, SWYER *et al.* 1961). Nor has it been shown that women of postmenopausal age with mammary cancer have a higher oestrogenic hormone excretion than those without (BROWN 1957, STRONG 1958). Moreover remarkable clinical improvement is induced by large doses of oestrogenic hormones, mainly in the postmenopausal age group (HADDOW *et al.* 1944, NATHANSON 1946). However the clinical benefits of castration, surgical or roentgenological, are generally recognized (SCHINZINGER 1889, BEATSON 1896, BOYD 1900, TAYLOR 1956, WALKER 1956, KENNEDY 1956, GORDON & SEGALOFF 1958, TREVES & FINKBEINER 1958, and others). It has been claimed that the clinical effect of castration may be improved by simultaneous administration of cortisone (NISSEN-MEYER & VOGT 1954—1959, BRINKLEY & KINGSLEY PILLERS 1960, PEARSON & RISHOLM 1960). Likewise androgen hormones are very widely used, but their side-effects are considerable (ULRICH 1939, LOESER 1939, PEARSON *et al.* 1954, ESCHER 1958 b, DANIEL 1961 and others).

The nortestosterone derivatives have a much less virilizing action, but a stronger anabolizing effect. Comparatively good results have been reported with norandrostenolone phenylpropionate (GERBRANDY & HELLENDOORN 1957, NOWAKOWSKI & PABADA 1958, MALMIO *et al.* 1960, HORTLING *et al.* 1961 and 1962), but also with other related compounds (Cf. p. 27).

On the whole, during the last few years a more critical evaluation of the patient series has revealed a lower percentage of favourable responses

MATERIAL AND METHODS

In this in estigation, 073 endocrine treatment courses were given to 472 patients suffering from metastasizing mammary cancer· the effect of 888 endocrine treatment courses on 375 patients could be uniformly evaluated. The duration of the metastatic stage of the disease was further considered in 121 patients not receiving any endocrine treatment at all. Not only the general results of the methods used (castration, usually roentgenological, cortisone, androgens, norandrostenolone phenylpropionate and decanoate, oestrogens in large doses and hypophysectomy), but also the order in which these treatments were employed, has been considered. We ha e also observed the relative merits of combined or separate treatment, and the correlation between the changes in the oestrogen effect in the aginal smear and the clinical effect. Furthermore, we have observed the survi al time from the onset of metastatic spread in three groups of patients: those showing fa ourable clinical reaction to endocrine treatment, those showing a poor clinical effect despite endocrine treatment, and a group consisting of 121 patients receiving no endocrine treatment at all.

The majority of the patients were *treated at the Department of Radio-*therapy Helsinki, where patients from all over the country are seen for post operative roentgen treatment as well as for local treatment of metastases. The hypophysectomies were performed at the Department of Neurosurgery (G B.). All vaginal smear samples were taken, stained and evaluated by the same investigator (L. H B.). The endocrinological supervision, especially before and after hypophysectomy was made by H. H. With a limited number of patients, both treatment and follow up took place at the Deaconess Hospital, II Med. Dept., where the hypophysectomized patients were also treated before and after the operation.

The methods of endocrine treatment were in general the same as have been employed in recent years by a number of other investigators

Castration was mostly done roentgenologically and only in 13 patients was surgical castration performed. The roentgen dose used was *1600 r on each* ovary measured on the skin. The treatment lasted 4 days on each ovary successively The *androgens* were gi en in doses corresponding to 50—100 mg. Testosterone *propionate three times weekly* *Cortisone* was given in daily doses corresponding to 10—15 mg. prednisolone in order to depress the adrenal cortical

(ESCHER 1958a) It seems that when used alone, no endocrine method gives results in which the favourable response much exceed 40 per cent. The average duration of the clinical improvement, when hypophysectomy and perhaps, castration are not included is generally not more than one year Until recently it has been considered questionable whether endocrine treatment really prolongs life. Careful evaluation, however has shown that a prolongation of survival time is probable when androgens or oestrogens as well as ablative procedures are used (HUSEBY 1958, Amer Subcommittee on Breast and Genital Cancer 1960 TAYLOR & PERLIA 1960) With endocrine therapy the clinical wellbeing of the treated patient is often striking and as a rule, enables her to resume work

The usefulness of prophylactic endocrine treatment at the stage of the primary tumour and before the onset of metastatic spread has been questioned (SEGALOFF 1958) but studies have been made that point to the value of prophylactic castration either alone (WINZ 1918 HORSLEY 1951 TREVES 1957 SIEGERT 1958) or combined with androgen (POPPE & CREGL 1961) or cortisone (NISSEN MEYER 1962) therapy or of androgens alone (SICARD & MARSAN 1958)

One cannot but feel that the endocrine methods of treatment of metastasizing mammary cancer have been more or less fully explored with regard to the frequency and duration of the periods of improvement. It is possible, however to reduce the side effects connected with the treatment or operative measures, as to some extent has already been done. The full use of all available endocrine methods of treatment, as well as the use of new active agents, may also prolong the life of the patients.

There are few reports considering the results of different endocrine treatments in the same series of patients, and a generally accepted scheme for the endocrine treatment of metastasizing mammary cancer is still not available

MATERIAL AND METHODS

In this investigation, 973 endocrine treatment courses were given to 472 patients suffering from metastasizing mammary cancer the effect of 888 endocrine treatment courses on 375 patients could be uniformly evaluated. The duration of the metastatic stage of the disease was further considered in 121 patients not receiving any endocrine treatment at all. Not only the general results of the methods used (castration, usually roentgenological, cortisone, androgens, norandrostenolone phenylpropionate and decanoate, oestrogens in large doses and hypophysectomy), but also the order in which these treatments were employed, has been considered. We have also observed the relative merits of combined or separate treatment, and the correlation between the changes in the oestrogen effect in the vaginal smear and the clinical effect. Furthermore, we have observed the survival time from the onset of metastatic spread in three groups of patients: those showing favourable clinical reaction to endocrine treatment, those showing a poor clinical effect despite endocrine treatment, and a group consisting of 121 patients receiving no endocrine treatment at all.

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function 40—50 mg of prednisolone were given as daily doses to 5 patients with brain metastases.

Norandrostenolone preparations were given as norandrostenolone phenylpropionate (Durabolin Organon) 25—75 mg every 7th to 10th day and as norandrostenolone decanoate (Deca-Durabolin Organon) in doses of 25—50 mg every 3rd or 4th week. *Oestrogens* were mostly given in the form of ethinyloestradiol (Follinyl Lääke Oy) in tablets of 0.5 mg The daily dose was 1—3 mg orally or sublingually *Hypophysectomy* was performed by the intracranial subfrontal route. After section of the pituitary stalk and emptying of the sella with curettes, the walls of the sella were cauterized with Zenker's solution, or electrocoagulated In patients with an extremely prefixed optic chiasm, one optic nerve had to be sacrificed, this occurred in a few of the earlier cases of the series. Later this was avoided by trephining the tuberculum sellae between the optic nerves. However visual field defects could not always be avoided. As a rule, the patients were given cortisone from the day before operation onwards, but in 10 cases adrenocorticotrophic hormone only was used. In these cases, clear signs of adrenocortical insufficiency such as fever and weakness, were always observed about one week after the operation. In the cases in which autopsy was performed remnants of the pituitary gland were found comparatively frequently The endocrinological symptoms of insufficiency of the peripheral glands have been reported previously In around three-quarters of the hypophysectomized patients, deficiency in the function of the thyroid gland and the ovaries appeared as a sequel to the operation. (HORTLING *et al* 1959 HIISI BRUMMER *et al.* 1960).

As a rule, the endocrine treatment was continued for 1—3 months before a negative effect was acknowledged, and longer than 3 months in cases responding favourably If the clinical state of the patient deteriorated, the treatment was sometimes interrupted even earlier and sometimes even despite subjective well-being, when signs of progressive metastatic spread were unmistakeable. In this series of patients, there was generally no interval between the different therapy courses. A so-called rebound effect (ESCHER & KAUFMANN 1960), produced by cessation of a hormone therapy was not observed. However this effect is claimed to be exceptional, and the duration of the improvement is brief (Amer Subcomm. on Breast and Genital Cancer 1960)

The evaluation of a clinical effect was founded on objective criteria only The roentgenologist (K.M) and the endocrinologist (H.H) decided jointly whether the clinical response to an endocrine treatment was favourable (objective improvement, or clinical arrest of an otherwise progressing disease), which means that all cases were uniformly interpreted The results of treatment were re-assessed after an interval of 1—2 years.

An objective sign of improvement was a decrease in the size of a lesion estimated roentgenologically or with the naked eye. Increased deposition of calcium salts as well as the disappearance of normoblasts in leucoerythroblastic anae-

mia, were also positive signs (HOHTLING *et al.* 1957). An apparent improvement in the general health simultaneously with a fall in the erythrocyte sedimentation rate and an improvement of an anaemic state, even when no apparent change in the size of metastases was observed, was sometimes considered indicative of objective improvement.

Progression of metastases inhibited simultaneously with an improvement in the general health was defined as arrest of the metastatic process. A small number of cases in which the progress of the disease was apparently slowed down compared with the course before and after the endocrine treatment in question, were also included in this group. The general condition of these patients showed marked improvement during the time that the arrest lasted.

Cases in which the disease progressed at the same speed as before the endocrine treatment were considered to be therapeutic failures, regardless of the subjective feelings of the patient. A purely subjective improvement was thus not regarded as a favourable response. This negatively responding group also includes cases in which the course of therapy lasted less than one month, but where the treatment had to be interrupted because of an apparent worsening of the disease, or because of severe side effects of the hormones used.

The endocrine treatment was administered to patients with significant signs of an active and progressive process when it was presumed that roentgen treatment only was not enough, or when a disseminated disease was apparent. Borderline cases in which it was not possible to exclude the effect of roentgen treatment, but in which the endocrine treatment was nevertheless thought to be of use, were placed in a separate group. It was thought that a wrong impression of the significance of the endocrine treatment might be obtained if these cases were not considered. On the other hand, 97 cases were not evaluated, because it was uncertain whether there had been a worsening of the disease or not, or because the effect of an endocrine treatment could not be evaluated, or because the treatment was given as a prophylactic measure and was not directed toward a metastatic process. Axillary metastases only were not considered as disseminated metastatic spread. In the 375 patients evaluated, 85 single therapeutic measures were not included for the reasons mentioned above. These measures were considered only when it had to be determined whether the patients had received endocrine treatment before or not.

In all cases, the diagnosis was verified histologically certainly at the beginning of the disease; and in many cases subsequently.

The clinical effect of treatment was followed not only by frequent roentgen investigations, but also by a general clinical examination including the peripheral blood picture, the erythrocyte sedimentation rate, the alkaline phosphatases in serum, the serum calcium, and the calcium excretion in the urine determined after 3—4 days on a milk and-cheese-free diet. For practical reason, however these last mentioned investigations could not always be made.

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RESULTS

In the following, the results of the treatment of metastasizing mammary cancer by different methods are given under separate headings. In order to ascertain the optimal sequence of the different treatment courses the results are given separately for each treatment, according to its place in the sequence.

CASTRATION SERIES

Castration was performed on 203 patients. A roentgenological procedure was used, with the exception of 13 cases in which a surgical oophorectomy was performed. The average age was 46 years (30—63).

It appeares from Table 1 that the results were clearly not so good when

TABLE 1

Clinical results of castration in 203 patients

		Objective improvement	Arrest	Poor effect	Favourable responses (per cent)	Favourable responses (total percentage)	Average age (years)
First course	Obvious castration effect	9	20	77	27.4	30.4	46.0
	Additional roentgen effect possible	3	18				
Second course	Obvious castration effect	1	1	18	10.0	14.3	44.8
	Additional roentgen effect possible	—	1				
Third course	Obvious castration effect	1	—	4	20.0		45.3
Castration additional hormone therapy	Obvious effect of endocrine therapy	10	8	23	43.9	54.0	
	Additional roentgen effect possible	2	7				
	Total	26	55	122		40.0	

studied in a large number of patients by means of the vaginal smear technique, previously described in detail by HIISI BRUMMER *et al* 1960 As a rule, several smears were taken during the evaluated treatment courses. The results of the vaginal smear investigation in a number of cases was directly used as a guide during the treatment with androgens. On 41 patients of 50 years or more with an oestrogenic effect apparent in the vaginal smear castration was performed Oestrogens were seldom used when an oestrogenic effect was apparent in the smear

The order in which the different endocrine therapy courses were given was not determined by any fixed rules. Castration was mostly performed as the first treatment, and hypophysectomy as the last resort, with androgens, cortisone and nortestosterone relatively often given in between but varying the order of administration

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	Additional roentgen effect possible	—	1				
Third course	Obvious castration effect	1	—	4	20.0	—	48.2
Castration additional hormone therapy	Obvious effect of adjuvant therapy	10	8	23	43.9	54.0	
	Additional roentgen effect possible	2	7				
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TABLE 3

Results of treatment with androgens in [illegible] patients

		Objective improvement	Arrest	Poor effect	Favourable responses (per cent)	Favourable responses (total percentage)	Average age (years)
First course	Obvious effect of androgen therapy	5	17	64	25.6	28.9	51.0
	Additional roentgen effect possible	—	5				
Second course	Obvious effect of androgen therapy	1	6	61	10.3	11.6	48.5
	Additional roentgen effect possible	—	1				
Third course		—	—	7	0		
Androgens + other endocrine therapy	Obvious effect of endocrine therapy	5	6	21	34.0	44.7	
	Additional roentgen effect possible	2	4				
	Total	13	[illegible]	153		25.4	
Patients 40—[illegible] years old							
First course		—	25	61		25.0	
Second course		—	3	18		14.3	

year-old patients the percentage was 28 (7/25) against 11.4 (5/44) in 51 to 59-year-old patients.

The duration of the favourable effect is seen in Table 4. It is possible that the comparatively long duration of the favourable effect in some groups is not statistically significant, as the effect in single cases varied considerably (4—28 *months*). In patients showing objective remission, the favourable effect lasted 10.0 months.

The side effects of androgens are often very disturbing, and in this series they seem to appear with the same frequency as had been reported by others. Hirsutism, eroticism, deepening of the voice, acne hypercalcemia etc. were all observed.

TABLE 4

Duration of favourable effect of androgen therapy

	Number of cases	Mean duration of favourable effect
First course	18	11.7 months
Second course	7	16.4
First course additional roentgen effect possible	3	16.5
Androgens + other endocrine therapy	9	15.4
Combined treatment, roentgen effect possible	6	13.0
Exclusively objective improvement	9	10.9

castration was performed as the second or third therapeutic measure. When castration was employed as the second manoeuvre, the *first* therapy had been androgens in 13 cases, cortisone in 1 roentgen castration prior to surgical castration in 2, *durabolin in 3* and oestrogens in 1 case. The number of patients that were castrated as the third manoeuvre was only 5 If the *second* and the third manoeuvres are combined the percentage of the cases *responding* favourably is only 12. If another endocrine therapy (cortisone, *androgens*, nor androstenolone phenylpropionate) was given in connection with castration the results *appeared* to be better than after castration only· however this group was small

TABLE 2
Duration of favourable effect f castration

	Number of cases	Mean duration of favourable effect
Obvious favourable effect	27	25 months
Additional roentgen effect possible	15	27 0
Simultaneous hormone treatment	13	17
Castration + other endocrine therapy + possible roentgen effect	10	11.3
Exclusively objective improvement	10	24.1

The duration of the therapeutic effect appears from Table 2. An interesting feature is that in the group of patients where a combined treatment had been given with a high number of favourable responses the duration of the period of *clinical* improvement was relatively short. This is probably explained by the fact that the combined form of treatment was *tried* mainly in cases with a rapid progression of the disease. Table 2 also shows *that the* duration of the therapeutic *effect* was not prolonged in the cases *where a* positive roentgen treatment effect was thought to have contributed to the *favourable* clinical response. This indicates that at this stage of the disease, the endocrine treatment is decisive for the duration *of* the *clinical* effect.

41 of the 203 castrated patients were 50—63 years old. A favourable clinical effect was seen in 13 patients (32%), the oldest of whom was 61

ANDROGEN SERIES

The number of the patients evaluated was 205 and the results *are seen in* Table 3. In the 66 patients to whom the androgen therapy was administrered as the second manoeuvre castration had been the first in 50 cases, cortisone in 7 oestrogens in 8 and durabolin in one There was a markedly decreased incidence of favourably reacting cases in the 2nd and 3rd therapy courses compared with the first course Androgens in combination with other endocrine treatment, mostly castration generally yielded better results. In a group of 105 patients in this androgen series, also including patients to whom other treatment had been given simultaneously but without effect, 70 were 51—68 years old and 35 younger The percentage of favourably responding cases was 17 in both groups. However in 60 to 68

TABLE 6

Results of cortisone treatment in 199 patients

		Objective improvement	Arrest	Poor effect	Favourable responses (per cent)	Favourable responses (total percentage)
First course	Obvious effect of cortisone therapy	2	—	24	7 7	14.3
	Additional roentgen effect possible	—	2			
Second course	Obvious effect of cortisone therapy	3	5	51	13.6	15.0
	Additional roentgen effect possible	—	1			
Third course	Obvious effect of cortisone therapy	4	9	49	21.0	22.2
	Additional roentgen effect possible	—	1			
Fourth course	Obvious effect of cortisone therapy	—	3	21		12.5
2nd—4th course after castration	Obvious effect of cortisone therapy	(4)	(9)	(66)	16.5	18.5
	Additional roentgen effect possible	(—)	(2)			
2nd—4th course after other endocrine therapy	Obvious effect of cortisone therapy	(2)	(6)	(53)		13.1
Cortisone and castration simultaneously	Obvious effect of endocrine therapy	1	3	8	40.0	57.1
	Additional roentgen effect possible	—	4			
	Total	10	28	161		20.1

TABLE 7

Duration of favourable effect in patients treated with cortisone

		Number of cases	Mean duration of favourable effect
First course	Obvious effect of cortisone therapy	2	10.0 month
	Additional roentgen effect possible	1	12.0
2nd—4th course after castration	Obvious effect of cortisone therapy	12	14.0
	Additional roentgen effect possible	2	7 7
2nd—4th course after other endocrine therapy	Obvious effect of endocrine therapy	8	6.2
Cortisone and castration simultaneously	Obvious effect of endocrine therapy	4	11.7
	Additional roentgen effect possible	4	9.0

TABLE 5

Clinical results of treatment with oestrogens in 65 patients

		Objective improvement	Arrest	Poor effect	Favourable responses (per cent)	Favourable responses (total percentage)
First course	Obvious effect of oestrogen therapy	6	4	25	28.5	31.2
	Additional roentgen effect possible	1	3			
Second course	Obvious effect of oestrogen therapy	1	1	1	13.3	
Third course		—	—	10	0	
	Total	7	8	50		23.1

OESTROGEN SERIES

Oestrogens were given to 65 patients from 54 to 78 years old. The results are seen in Table 5. Two patients given oestrogens without effect after hypophysectomy are not included in the table. As in both the previous series, results were less good when the treatment was not given as the first. Nine patients who did not tolerate oestrogen hormone treatment, which had to be interrupted, are included among the negatively responding cases. The side effects consisted of irregular bleedings, anorexia, dyspeptic troubles, etc. However recourse to other oestrogen preparations might have reduced the incidence of side effects.

The average duration of the favourable effect was 12.9 months in 10 cases evaluated but 15 months in 8 cases where oestrogens were given as the first manoeuvre.

CORTISONE SERIES

Cortisone was used in altogether 180 cases, in order to depress adrenocortical activity. Large doses were used in 5 patients with brain metastases, with a good result in one. The results of the cortisone treatment are to be seen in Table 6. A remarkable feature is the tendency towards better results when cortisone was not given as first treatment but at a later stage. Results were particularly good when castration had been the first treatment, but were also satisfactory after other kinds of endocrine treatment.

The mean duration of the favourable effect in cortisone treated patients, varying between 1 and 11 months is shown in Table 7.

In only 2 cases did the side effects of cortisone preparations result in an interruption of the treatment. The generally accepted principles for the use of cortisone were followed.

NORTESTOSTERONE DERIVATES

NORANDROSTENOLONE PHENYLPROPIONATE SERIES

The results in 128 cases treated with norandrostenolone phenylpropionate (n.a.p.p. Durabolin Organon) are seen in Table 8, and the duration of the favourable effect in Table 9. The effect of this

et al. 1959, HORTLING *et al.* 1961). The duration of the clinical effect was roughly the same as after androgens. The side effects of n.a.p.p. were less disturbing than those seen in connection with androgen therapy. The treatment had to be interrupted because of acne in one case and dyspnoea and distress in 2. (Cf. HORTLING *et al.* 1961). Hypercalcemia causing clinical symptoms was not observed.

NORANDROSTENOLON DECANOATE SERIES

This preparation (Deca-Durabolin Organon, n.a.d.) with even less androgenic and more powerful anabolic properties than norandrostenolone phenylpropionate, was given to 42 patients, and the results could be evaluated in all cases (Table 10). To 8 patients it was given as the first manoeuvre, and a favourable effect was seen in 3 (37.5%). In the remaining 31 patients, it was given as the 2nd to 5th treatment. An objective favourable clinical effect was noticed in 9 of these 31 patients (32%). In two previously hypophysectomized patients n.a.d. was ineffective. N.a.d. was effective sometimes when durabolin was ineffective, or when a favourable effect of n.a.p.p. had faded away. The duration of the clinical effect with n.a.d. in the 7 patients in whom an evaluation of the duration was possible, was 7 months on the average. This figure may however be regarded as misleadingly low as the clinical effect observed is still present in some patients.

The patients tolerated n.a.d. very well, no side-effects at all were reported by the patients and the therapy did not have to be interrupted in a single case. A more detailed comparison between the effect of androgens, n.a.p.p. and n.a.d., in the treatment of metastasizing mammary cancer has been given recently (HORTLING *et al.* 1962).

HYPOPHYSECTOMY

Our preliminary results have been reported previously (HORTLING *et al.* 1957 1958, 1960).

The clinical results in 63 cases of hypophysectomy are given in Table 11

TABLE 10

Results of treatment with norandrostenolone decanoate in 42 patients

		Objective improvement	Arrest	Poor effect	Favourable responses (per cent)	Favourable responses (total percentage)
First course	Obvious effect of endocrine therapy	1	2	5	37.5	
2nd—4th courses	Obvious effect of endocrine therapy	—	9	22	32.1	34.1
	Additional roentgen effect possible	—	1			
Previously hypophysectomized patients		—	—	2		0

TABLE 8

Results of treatment with norandrostenolone phenylpropionate in 126 patients

		Objective improvement	Arrest	Poor effect	Favourable responses (per cent)	Favourable responses (total percentage)
First course	Obvious effect of endocrine therapy	5	2	16	30.1	40.7
	Additional roentgen effect possible	—	4			
Second course	Obvious effect of endocrine therapy	2	4	22	21.4	33.3
	Additional roentgen effect possible	—	5			
Third course	Obvious effect of endocrine therapy	2	6	35	18.6	20.5
	Additional roentgen effect possible	—	1			
Fourth course	Obvious effect of endocrine therapy	3	1	6		10.0
	Total	12	23	79		30.7
Previously hypophysectomized cases		—	—	12		0

TABLE 9

Mean duration of favourable effect in patients treated with norandrostenolone phenylpropionate

	Number of cases	Mean duration of favourable effect
First course	7	12.3 months
Second third, fourth courses	16	10.1
Exclusively objective improvement	9	11.6

treatment has been reported previously by members of this group (MALMIO *et al.* 1959 HORTLING *et al.* 1961 1962) Most of the cases were re-assessed while this study was in preparation and some changes in the clinical evaluation were made. This depends on the *fact that in* the first evaluation the clinical effect was *still going on in some patients and a* re-assessment later sometimes showed that what had *at first* been *taken for* a clinical improvement could not be *confirmed later In some cases* a supposed metastatic spread proved not to have been *metastasis* at all. However the results reported here agree in the main with our original evaluations.

An interesting feature is the fact that the response to n.a.p.p. was comparatively good even when it was administered as a later treatment, which was not the case when *androgens* were used. N.a.p.p. also had a positive effect *in a number of cases in which the good* effect of androgens had ceased or where *they had had no effect at all* (MALMIO

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2nd—4th courses	Obvious effect of endocrine therapy	—	8	22	32.1	34.1
	Additional result no effect possible	—	1			
Previously hypophysectomized patients		—	—	2		0

TABLE 8

Results of treatment with norandrostenolone phenylpropionate in 1 8 patients

		Objective improvement	Arrest	Poor effect	Favourable responses (per cent)	Favourable responses (*total percentage*)
First course	Obvious effect of endocrine therapy	5	2	16	30.4	40.7
	Additional roentgen effect possible	—	4			
Second course	Obvious effect of endocrine therapy	2	4	22	21 4	33.3
	Additional roentgen effect possible	—	5			
Third course	Obvious effect of endocrine therapy	2	6	35	18.6	20.5
	Additional roentgen effect possible	—	1			
Fourth course	Obvious effect of endocrine therapy	3	1	6		40.0
	Total	12	23	79		30.7
Previously hypophysecto-mized cases		—	—	12		0

TABLE 9

Mean duration of favourable effect in patients treated with norandrostenolone phenylpropionate

	Number of cases	Mean duration of favourable effect
First course	7	12.3 months
Second third, fourth courses	16	10.1
Exclusively objective improvement	9	11 6

treatment has been reported previously by members of this group (MALMIO *et al.* 1959 HORTLING *et al.* 1961 1962). Most of the cases were re-assessed while this study was in preparation, and some changes in the clinical evaluation were made. This depends on the fact that in the first evaluation the clinical effect was still going on in some patients and a re-assessment later sometimes showed that what had at first been taken for a clinical improvement could not be confirmed later In some cases a supposed metastatic spread proved not to have been metastasis at all. However the results reported here agree in the main with our original evaluations.

An interesting feature is the fact that the response to n.a.p p was comparatively good even when it was administered as a later treatment, which was not the case when androgens were used. N.a p.p also had a positive effect in a number of cases in which the good effect of androgens had ceased or where they had had no effect at all (MALMIO

TABLE 12

Correlation between response to hypophysectomy and results of previous therapy

	Response to castration		Response to androgens		Response to cortisone		Response to s.a.p.p.	
	Good	Poor	Good	Poor	Good	Poor	Good	Poor
Patients with favourable response to hypophysectomy	4	7	1	7	2	8	1	3
Patients with poor response to hypophysectomy	6	20	5	17	4	17	0	9

of the patients in the beginning of our series died, because extra cortisone was not added in acute infectious states. These cases were not included in the calculation of the duration of the clinical response. Although metastasizing may be very advanced, the response may still be favourable. Within the first two days after the operation, two deaths occurred; the operative condition of these patients was extremely poor. Patients with large metastases of the lungs causing respiratory insufficiency did not sustain operation under general anaesthesia well; in such cases, local analgesia in combination with large doses of a lytic cocktail (chlorpromazine + promethazine + pethidine) administered intravenously was better tolerated.

TABLE 11

Clinical results of hypophysectomy in 43 patients

	Objective improvement	Arrest	Poor response	Percentage of favourable responses
First treatment course	2	1	3	50
Second	3	—	5	37.5
Third	4	1	15	25
Fourth	4	2	18	25
Fifth	1	1	3	40
Total	14	5	44	30
Patients under 50 years *)	12		23	34
Patients 50 years or over*)	7		8	47

*) Only patients surviving more than 14 days after operation.

Of the 44 patients in whom poor results were observed, 13 died within two weeks after the operation. If these cases, where a direct stressing effect of the operation may have contributed to the fatal out come, are omitted the percentage of improved cases rises to 47.5. There was no significant difference in the clinical effect above or below the age of 50

The mean duration of the improvement or the arrest in the 16 cases in which it could be evaluated, was 19 4 months (5—36 months), or more, as 3 of these patients are still alive. The mean duration of the improvement in the three patients on whom hypophysectomy was performed as the first treatment, was 25 4 months (one patient is still alive)

It has also been stressed by others that the clinical effect of hypophysectomy when performed as first treatment may last longer than when performed at a later stage (PEARSON & RAY 1960) The evaluation of our results in the different groups of hypophysectomized patients is, of course, somewhat uncertain, as the number of patients is comparatively small in the different groups. However there was an evident tendency towards good results, even when the hypophysectomy was performed after other kinds of endocrine treatment.

Some interest has been focused on the correlation between the clinical response to hypophysectomy and the effectiveness of previously given endocrine treatment manoeuvres (PEARSON et RAY 1960). The results in this respect are presented in Table 12. Cases in which the patient died within two week after the operation are omitted from the table. The observations support the opinion that if the response to a previous oophorectomy or castration has been good it is more likely that the response to hypophysectomy will be favourable. Thus, the ratio of positive to negative responses to previous castration was 0.57 (4/7) in the group in which hypophysectomy was effective and 0.3 (6/20) when the response was poor With regard to previous androgen therapy the same ratios were 0.13 (3/7) and 0.29 (5/17).

As a rule, there was no difficulty in managing the patients after hypophysectomy It appears probable that two

SURVIVAL OF PATIENTS. GENERAL OBSERVATIONS

The survival time from the appear ance of metastases to the death of the patients, was compared in patients showing a favourable response to an endocrine treatment, patients showing no clinical response, and patients who had not received any endocrine treatment at all. All the patients had had roughly the same roentgen therapy The patients not receiving endocrine therapy had been treated at the Department of Radiotherapy during the years 1939—1953. The results are gi en in Table 13. From the table, it appears that the survival time after the onset of metastases was significantly longer in patients who responded well to endocrine treatment than in those with poor response to endocrine therapy and in patients that *had received no endocrine therapy* Patients who responded positively to tw or even more treatments, 19 and 3 patients respectively again showed a significantly longer survival time, the increase corresponding to the duration of a second clinical response. The number of patients with more than one clinical response was, however small compared with the number of patients with only one good clinical response. The percent age of survivors at different times after the beginning of the metastatic stage of the disease, is seen in Fig. 2. Patients with clinically favourable response show a higher percentage of survivors.

The following figures concerning the probability of a favourable clinical response to the endocrine therapeutic measures used, are also of interest. 162 out of 375 patients considered, or 43.2 per cent, responded to at least one of the endocrine manoeuvres used. Ninety nine patients, showing a favourable response to the first endocrine treatment

TABLE 13

Correlation between survival time from first appearance of metastases and clinical response to endocrine treatment

	Number of cases	Mean age years	Mean survival time from first ppearance of metastases to death of patient
One favourable response to endocrine treatment	77	49.8	25.3 months
T or more favourable responses	22	49.2	40.1
No favourable response	77	43.0	14.1
No endocrine treatment given	121	53.3	14.8

COMPARISON OF THE RESULTS OF DIFFERENT KINDS OF TREATMENT AND CONSIDERATION OF THE ORDER OF ADMINISTRATION

This comparison is made graphically (Fig 1) The percentages of *favourable responses* are given separately depending on which course of treatment was employed and the order in which it was given. In this comparison cases are not *included in* which the roentgen treatment may have contributed to a *favourable clinical* response. *It* is apparent that the effect of castration androgens and oestrogens significantly decreases if the treatment is given as the second man oeuvre or later Norandrostenolone phenylpropionate, decanoate as well as hypophysectomy on the other hand are quite effective even at later stage, although the results of the first course seem to be the best. Cortisone on the contrary induces very few *favourable* responses when given as the first treat ment, but an increasing number of favourable responses when employed as the second or the third treatment course

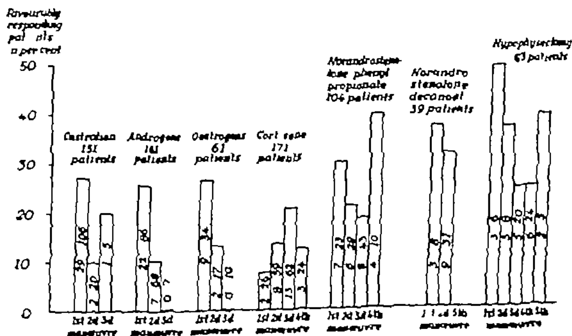


Fig. 1 Results of 730 endocrine treatment courses grouped according to the ord of pplication The higher figures within the columns indicate the numbers of patient tre ted and th lower those responding fa ourably

SURVIVAL OF PATIENTS. GENERAL OBSERVATIONS

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The following figures concerning the probability of a favourable clinical response to the endocrine therapeutic measures used, are also of interest. 102 out of 375 patients considered or 43.2 per cent, responded to at least one of the endocrine manoeuvres used. Ninety nine patients, showing a favourable response to the first endocrine treatment

TABLE 13

Correlation between survival time from first appearance of metastases and clinical response to endocrine treatment

	Number of cases	Mean age years	Mean survival time from first appearance of metastases to death of patient
One favourable response to endocrine treatment	77	49.8	24.3 months
Two or more favourable responses	23	49.3	30.1
No favourable response	77	53.0	14.1
No endocrine treatment given	121	53.3	14.6

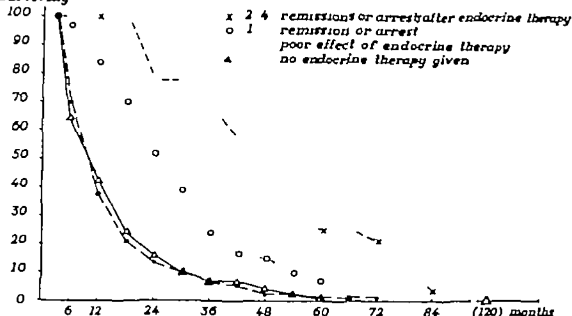


Fig. 2. Number of surviving patients in per cent at different time intervals after beginning of the metastatic spread.

given, received a second treatment, 38 of them responding favourably (38.4%). Twenty-one of these 38 were given a third endocrine treatment, 9 of them (43%) responding favourably. Thus, the chances of a patient responding favourably to endocrine treatment are no greater when he has once or twice before responded well to another such therapy.

CORRELATION BETWEEN THE CHANGES OF THE OESTROGENIC EFFECT IN THE VAGINAL SMEAR AND THE CLINICAL RESPONSE

The biological oestrogenic effect was followed in a number of patients during the course of different endocrine therapeutic procedures. The results of such a comparison have been reported previously in connection with hypophysectomy and treatment with norandrostenolone phenylpropionate (Hirst-Brunner *et al.* 1960, Malmio *et al.* 1959 Hortling *et al.* 1961).

The results of this study are reported in Table 14. It must be taken into account that when a decrease in the biological oestrogenic effect was conceded, those cases are, of course, not included in which no oestrogen effect was observed at the beginning of the treatment. On the other hand, they were considered when an increase in the oestrogenic effect was conceded.

In the table, the number of cases in which no biological oestrogenic effect was observed at the beginning of the therapy is mentioned separately. In the castration, the androgen, and the hypophysectomy groups, there was no clear correlation between a favourable clinical response and a decrease of the oestrogenic effect. An increase of the oestrogenic effect was very rare in these groups. In the norandrostenolone phenylpropionate and the cortisone groups, clinically favourably responding patients showed a decrease in the oestrogenic effect slightly

TABLE 14

Correlation between changes in level of oestrogenic effect in vaginal smear and clinical response to endocrine therapy

Therapy used	Number of cases evaluated	Number of cases without oestrogen effect visible in vaginal smear	Frequency in per cent of decrease in oestrogen effect		Frequency in per cent of an increase in oestrogen effect	
			Favourable response	Poor response	Favourable response	Poor response
Castration	92	2	71.4	81.4	2.9(1/35)	12.3(7/57)
Androgens	113	7	51.7	64.2	10.3(3/29)	4.8(4/84)
Norandrostenolone phenylpropionat	1	9	61.9	36.7	4.8(1/21)	3.3(1/30)
Cortisone	77	23	31.8	12.7	13.6(3/22)	27.3(15/55)
Oestrogens	23	10	—	—	100	100
Hypophysectomy	25	20	73.0	33.0	0	0

more frequently than patients in whom no clinical effect was recorded An interesting feature, however was that an increase of the oestrogenic effect seemed to be comparatively common during the course of cortisone administration (27 1%) especially when no clinical response was obtained. 8 of the 18 patients in whom cortisone treatment caused an increase in the oestrogenic effect, had been previously castrated roentgenologically

The oestrogen therapy caused a strong increase in the oestrogenic effect in the vaginal mucous membranes and this was, of course, to be expected. The cases responding favourably to oestrogen therapy showed no oestrogenic effect at the beginning of the therapy and among 20 patients with a poor response to oestrogen therapy 1 showed signs of an oestrogenic effect in the vaginal smear

DISCUSSION

It is hoped that the observations made in this study may contribute towards a simpler scheme for the treatment of metastasizing mammary cancer

It must be stressed that in this comparatively large series of patients no regular randomisation was possible in the determination of endocrine treatment courses. Each method was used as the first therapeutic approach on a comparatively large number of patients. As second and third treatments, androgens, castration or cortisone, and during recent years even norandrostenolone phenylpropionate and decanoate, were *the commonest, without favouring any* particular treatment. In patients of postmenopausal age, oestrogen therapy was mostly the first treatment, but androgens and castration were also used when the vaginal smear indicated a persistent oestrogenic effect. Hypophysectomy was mostly performed as a last resort, but sometimes when the disease seemed to progress rapidly it was thought that thi ablative method should be employed earlier

This body f data thus represents the *results of treatment schedules based* on a compromise between randomisation and the following of insecurely established principles. Consequently the data are not treated statistically It is also important that all evaluation of clinical effects was checked by two members of the team, one representing radiology and the other internal medicine and endocrinology. *It seems probable* that the results of the endocrine treatment used have a general bearing, the more so as some of the features observed were obvious.

The results of *castration* are comparable with other reported results, the positive effect varying between 15 and 50 per cent, whether castration was surgical or radiological (LETT 1905, BOYD 1900, WALKER 1956, TAYLOR 1956, KENNEDY *1956, TREVES 1957 GORDON & SEGALOFF* 1958). The mean duration of the clinical effect varies between 10 and 14 months in these reports. In this study the duration of the favourable effect was longer on an average 25 months when performed as the first endocrine treatment. This remarkably long duration may partly be explained by the fact that a comparatively large number of patients were at the early stages of the metastatic process, and a number were cases with metastatic spread outside the axillary region to the lymph nodes only In this study a clinical effect lasting less than 6 months was seldom regarded as a favourable response, as a remission of shorter duration is often difficult to

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poor. Its usefulness, however seemed to increase when cortisone was given as a second manoeuvre after either castration or androgens, and even further when given as the third manoeuvre after castration and a subsequent androgen course. This reaction was quite the opposite to that following castration or androgen therapy when administered after other previous endocrine therapy. It was *found that when cortisone was* administered immediately following upon castration, in the same manner as reported by NISSEN-MEYER & VOGT and NISSEN-MEYER (1954—61), our results *were similar to those of these authors.* However in our series, the duration of the favourable responses was shorter. This may be explained by the fact that we used this combined therapy only in *cases with a very rapidly progressing* disease. NISSEN-MEYER reported a duration of the favourable effect of 16 months (1961), which corresponds to the results our team achieved with castration alone. *Cortisone in large doses has also been* tried on patients with brain metastases (KOFMAN *et al.* 1958), and on cachectic patients in the final stage, either alone (PEARSON *et al.* 1955 LEMON 1957 STOLL *1960), or together with thyroxin (THAL-*MANN & MOESCHLIN 1956), but on the average the remission lasted only a few months. In one patient out of 4 with brain metastases treated with large doses of prednisolone we observed a striking effect lasting 11 months.

Norandrostenolone phenylpropionate (Durabolin Organon) was given to 126 patients in this series. As has been reported (MALMIO *et al.* 1959 HORTLING *et al.* 1961 1962), this preparation has far fewer side effects than the traditional testosterone preparations. Virilisation was *rather infrequent* and, when it occurred, slight, and hypercalcemia was not observed either. The anabolic properties are greater than those of testosterone derivatives (VAN DER WERFF 1958). Our results with *norandrostenolone phen*ylpropionate appeared to be somewhat better than those with androgens, *showing* a higher frequency of favourable responses; of special interest is the observation that this nortestosterone preparation was effective even when used after other therapy (Fig. 1), with *the exception of hypophysectomy.* This seems to indicate that norandrostenolone phenylpropionate is suitable as a treatment in the interval between castration and hypophysectomy and clearly *preferable to the traditional androgen* therapy.

The number of patients treated with other newer androgen derivatives in most reported series is small, but these series *usually contained randomized* patients. The results in a number of such trials are interesting. SEGALOFF *et al.* (1955), found objective improvement in 8 out of 34 patients (23.4%) treated with *dihydrotestosterone propionate.* Virilization, however occurred comparatively frequently. BLACKBURN & CHILDS (1959), studied the effect of methyldihydrotestosterone on 27 patients and saw *objective regression of the cancerous* process in 44 per cent. They found that the virilizing properties were less pronounced than those of testosterone propionate. SEGALOFF *et al.* (1960), reported *promising results* with Δ^1 testolactone on 7 out of 23 patients with

evaluate. In the cases progressing rapidly where other treatment was given simultaneously the effect lasted only 11.3 months. There were fewer favourable clinical results when castration was performed after previous treatment of another type mostly androgens.

Further it was interesting that castration also in this material seemed to be as effective in the postmenopausal period as before the menopause, when performed on patients showing signs of a persistent oestrogenic effect in the vaginal smear

The *androgen* therapy was effective almost in the same frequency as castration, but the effect lasted for a shorter time, on an average 11 7 months, when androgens were given as the first treatment. The results are comparable with other previous reports (WEST *et al* 1951 TAYLOR 1956 LEWISON *et al* 1956 HUSEBY 1958, MARTZ 1960 SEGALOFF 1960 LUFT 1961). The clinical effect of androgens seems to be better during the later postmenopausal period than during the first 9 years after the menopause, this has also been stated by The American Subcommittee on Breast and Genital Cancer (1960) The clinical effect of androgens when given as the second or third manoeuvre, mainly after castration and cortisone, was not very satisfactory Moreover taking into account the very distressing side effects that are connected with the use of androgens, to some extent noticeable even when oral preparations such as fluoxymesterone (KENNEDY 1958, LOWE *et al.* 1961) are used it seems that there is no reason to employ this therapy as a second or third treatment. As the first treatment, on the other hand castration is to be preferred, as its effect apparently lasts longer and there are comparatively few side effects. For the same reasons, cortisone is preferable as a treatment applied simultaneously with castration. Conversely in patients of postmenopausal age, oestrogen hormones are preferable (Cf The American Subcommittee on Breast and Genital Cancer 1960) Thus, on the whole, there does not seem to be enough evidence in favour of the use of androgens as a regular method in the treatment of metastasizing mammary cancer

With regard to the frequency of positive responses, the clinical effect of the *oestrogens* during the postmenopausal period was much the same as that of androgens but the effect appeared to last longer Oestrogen hormones were not always well tolerated and the treatment had sometimes to be interrupted in this series in 9 patients out of 65 These were regarded as negatively responding cases. However the number of patients tolerating oestrogens was sufficient to make this treatment preferable to the use of androgens. The effect in different age groups was not separately analyzed because of the small number of patients. Our results correspond to those of previous investigators (TAYLOR 1956 LEWISON *et al* 1956 HAYWARD 1957 HUSEBY 1958). We did not use oestrogens on patients of premenopausal age, as some investigators have suggested

The clinical effect of *cortisone*, when administered alone in moderate doses as the first manoeuvre in order to suppress the adrenal cortical function, was rather

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Norandrostenolone phenylpropionate (Durabolin Organon) was given to 126 patients in this series. As has been reported (Malmio *et al.* 1959, Hortling *et al.* 1961, 1962), this preparation has far fewer side effects than the traditional testosterone preparations. Virilisation was rather infrequent and when it occurred, slight, and hypercalcemia was not observed either. The anabolic properties are greater than those of testosterone derivatives (van der Werff 1958). Our results with norandrostenolone phenylpropionate appeared to be somewhat better than those with androgens, showing a higher frequency of favourable responses; of special interest is the observation that this nortestosterone preparation was effective even when used after other therapy (Fig. 1), with the exception of hypophysectomy. This seems to indicate that norandrostenolone phenylpropionate is suitable as a treatment in the interval between castration and hypophysectomy and clearly preferable to the traditional androgen therapy.

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advancing breast cancer using 100 mg 3 times a week intramuscularly The *same group* (1959 a) reported 2 favourable responses with 4-oestrone-17 β-ol-3-one in 18 treated patients. JONSSON *et al.* (1959) observed 7 objective favourable responses in 34 patients treated with 9-α-brome-11 β-ketoprogesterone, but the effect lasted only 5 ½ months on an average. SEGALOFF *et al.* (1959 b), tried epitestosterone propionate on 18 patients, only one of them showing an objective favourable *response*, androsterone on 22 patients with only one short objective remission and androstanediol dipropionate on 24 patients, with objective favourable response in 1 (SEGALOFF *et al* (1960) DOUGLAS *et al* (1960) used 19-nortestosterone oenanthate on 12 patients, with remission in one. This preparation was shown to depress the gonadotrophin excretion whereas testolactone did not. LEWIN *et al* (1959) tried 17-ethinyl-19-nor testosterone on 22 patients, with remission in 5 More detailed reports are to be found in the Proceedings of the Conference sponsored by the Cancer Chemotherapy National Service Center edited by PINCUS & VOLLMER (1960) In none of the above mentioned series of patients is the rôle of a previous castration uniformly considered, nor is there any evaluation of these preparations as intermediate treatments.

In the present series of 42 patients, *norandrostenolone decanoate* seemed to be as effective as phenylpropionate. Thus decanoate appears to be suitable as an interim treatment.

A rough calculation based on available data concerning the androgenic and the anabolic properties of the androgen derivatives used in this study showed that in this series of patients, the clinical effect was probably not associated with the androgenic properties of the testosterone and nortestosterone preparations used (HORTLING *et al.*, 1962) On the other hand, the experiences of others in animal experiments (SEGALOFF 1958) show that a reduction of the virilizing propensity has invariably been associated with a reduction of the antitumour effect.

Although the number of *hypophysectomized* patients was limited, Fig 1 seems to show that this ablative measure is most suitable as a final method in the treatment of metastasizing breast cancer Perhaps operation yields a better result when performed as the first manoeuvre than when performed later but the effect does not last much longer in this series at least 21 months and 19 months respectively A few patients in both series are still alive. No other treatment has been proved effective after the favourable effect induced by hypophysectomy has receded which is an argument favouring hypophysectomy as the last treatment, (Table 12, Fig 2).

Interest has been focused on the problem of finding criteria for the selection of patients suitable for hypophysectomy In this series, patients of premenopausal age did not respond better than older patients, as was found to be the case by MCCALISTER *et al.* (1961) It has been claimed that a favourable effect of hypophysectomy is more frequent in patients responding well to a previous endocrine therapy especially castration (PEARSON & RAY 1960) some investigators how

ever have failed to detect any such clear correlation (McCALISTER et al. 1961). In the present series, there was a tendency towards better response to hypophysectomy in patients responding favourably to another form of endocrine therapy previously. BULBROOK et al. (1960) have suggested that the determination of 17-OH-corticoids and etiocholanolone is an aid to the prediction of the results of hypophysectomy but this has not yet been substantiated. Neither has the *determination of the excretion of gonadotrophins* and 17-ketosteroids proved helpful, from a practical point of view in this respect, nor has it helped in predicting the effect of other endocrine treatment, although much work has been devoted to this problem (HOBKIRK 1958, BIRKE et al. 1958, LORAINE et al. 1961 BORSEN et al. 1961).

Adrenalectomy combined with oophorectomy was not included in the methods used in this study because it was felt to be more advisable to obtain more experience with one ablative method, hypophysectomy than inconclusive evidence from two methods. It seems, however that the results obtained by other investigators using adrenalectomy and oophorectomy are not as good as those obtained with hypophysectomy either in regard to frequency of favourable response, or *duration of the induced* favourable effect, even the incidence *of operative complications is less after* hypophysectomy (PEARSON et al. 1958, 1960 ATKINS et al. 1960). *Identical* regression rate and survival after hypophysectomy and *adrenalectomy* respectively was recently reported by the Joint Committee on Endocrine Ablative Procedures in Disseminated Mammary Carcinoma *of the American Colleges* of Physicians and of Surgeons (1961). Hypophysectomy abolishes the secretion of growth hormones, which speaks in favour of this operation; it will, perhaps, also be possible to replace hypophysectomy by other nonoperative or operative procedures as, *e.g.*, high energy alpha particle beams (CONSTABLE et al. 1961), radioactive gold (BAUER & KLAR 1958) or implantation of radioactive yttrium (GLEADHILL 1956), when such procedures have been further developed. Many *investigators* have *reported* a duration of the favourable effect after adrenalectomy of 8—12 months (DAO & HUGGINS 1955 CADE 1955, HELLSTRÖM 1958), whereas the effect after hypophysectomy was reported to last 13—16 months (PEARSON & RAY 1960, OLIVECRONA 1961). PERLIA et al. (1956) saw a worthwile palliative effect after adrenalectomy only in 22—26% of 58 patients treated. ESCHER (1958 a), claims that results with adrenalectomy + oophorectomy are not better than those attained with oophorectomy alone; he does not recommend adrenalectomy + oophorectomy as the first treatment when metastases occur. Furthermore, the results of the combined treatment, castration + cortisone as a chemical adrenalectomy (NISSEN-MEYER & VOGT NISSEN-MEYER 1954—61 BRINKLEY & KINGSLEY PILLERS 1960), lasting at least as long, *seem to be comparable with the best reported results obtained with adrenalectomy* and oophorectomy.

In this study endocrine treatment courses where a simultaneous *roentgen*

advancing breast cancer using 100 mg 3 times a week intramuscularly The *same group* (1959 a) reported 2 favourable responses with 4-oestrone-17 β-ol-3-one in 18 treated patients. JONSSON *et al* (1959) observed 7 objective favourable responses in 34 patients treated with *9-α-brome 11 β-ketoprogesterone*, but the effect lasted only 5 ½ months on an average. SEGALOFF *et al* (1959 b) tried epitestosterone propionate on 18 patients, only one of them showing an objective favourable response, androsterone on 22 patients with only one short objective remission and androstanediol dipropionate on 21 patients with objective favourable response in 1 (SEGALOFF *et al* (1960) DOUGLAS *et al* (1960) used 19-nortestosterone oenanthate on 12 patients, with remission in one. This preparation was shown to depress the gonadrotrophin excretion, whereas testolactone did not. LEWIN *et al.* (1959) tried 17-ethinyl 19-nor testosterone on 22 patients, with remission in 5 More detailed reports are to be found in the Proceedings of the Conference sponsored by the Cancer Chemotherapy National Service Center edited by PINCUS & VOLLMER (1960) In none of the above mentioned series of patients is the rôle of a previous castration uniformly considered nor is there any evaluation of these preparations as intermediate treatments.

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in the liver and, to a certain extent, in the central nervous system, appear to respond less favourably to endocrine treatment than do metastases in other locations. Figures representing the incidence of a favourable clinical effect in patients with metastases in different organs are very difficult to compare and to evaluate. As a rule, metastases appear simultaneously in different locations; negative results of an investigation, however thorough, of the liver the skeleton, or even the lungs do not exclude the existence of metastases. Comparatively speaking, the localization of metastases was the same in later treatment courses employing different methods, and consequently did not influence the observed results.

It now seems likely that the employment of endocrine therapy means a prolongation of life. The report of the American Subcommittee on Breast and Genital Cancer shows this to be true with regard to androgens and oestrogens. In the present study the time from the first appearance of a metastasis to the death of the patient was, on an average, 28 months when one favourable response was noted, and 50 months when two or more favourable responses to treatment were observed. The difference between these groups and the group that did not respond to endocrine therapy is apparently significant. Fig 2 shows that the percentage of patients surviving for different lengths of time after the appearance of metastases, was higher in the group responding favourably to endocrine treatment once than in the negatively responding or untreated groups, and this was even more evident when there had been two remissions. The survival time after the onset of metastases was almost equally long in the group of 121 patients receiving no endocrine treatment whatsoever as in the group of patients reacting negatively to endocrine therapy- both groups received roughly the same amount of roentgen treatment.

Addendum In a recent report (RATZKOWSKI E. & HOCHMAN A., Cancer *14* (1961) 300) concerning 270 endocrinologically treated patients with metastasizing mammary cancer the mean survival time after recurrence was 20.2 months in patients who received hormone therapy and 14.5 months in patients who did not. In our series the corresponding figures were 24.8 and 14.8 months.

treatment may have contributed to a favourable clinical effect have been grouped separately. As a rule the duration of the beneficial effect in such cases was not significantly longer than in cases where the hormone effect was undisputable. Thus, the reported number of cases (in Tables 1, 3, 5, 6 and 8) with clear objective improvement or arrest may be too low rather than too high.

It has already been mentioned that some recent observations have shown that a relation between clinical response and decrease in oestrogenic effect in the body after castration or hypophysectomy is questionable (STRONG *et al.* 1956, BULBROOK *et al.* 1958, GORDON & SEGALOFF 1958, HULT BRUMMER *et al.* 1960, MC ALLISTER *et al.* 1960). Neither castration nor castration + adrenalectomy eliminate the oestrogenic effect (STRONG *et al.* 1956, BULBROOK *et al.* 1958, DICZFALUSY *et al.* 1959, HORTLING & HULT BRUMMER 1960). When using the vaginal smear method for the estimation of the biological oestrogenic effect in the body, the experiences in this series of patients revealed no significant parallellism between a favourable clinical effect and a decrease in the biological oestrogenic effect, either after hypophysectomy or after androgen therapy. An insignificant tendency towards some correlation was observed after norandrostenolone phenylpropionate, cortisone and, perhaps, castration. It was interesting that during the administration of cortisone, the oestrogenic effect clearly increased more often than during other non-operative treatments, or after castration or hypophysectomy. This increase seemed to be more frequent during androgen therapy than during norandrostenolone phenylpropionate administration, thus confirming previous reports, (MEYER 1955). It must be added that in 8 out of 18 cases where an increase in the oestrogenic effect was observed during cortisone treatment, castration had been performed previously. This seems to indicate that the increase in the oestrogenic effect is of adrenal origin despite the fact that cortisone induces a depression of the adrenal hydroxycorticosteroid production. An increase in gonadotrophin secretion is probable after cortisone treatment, (LEMON 1957, SEGALOFF 1958). An apparently favourable clinical effect after castration was observed once in conjunction with a rise in the oestrogenic effect. On the other hand we found that after hypophysectomy the oestrogenic effect sometimes reappeared simultaneously with recurrence of the disease (HORTLING *et al.* 1957).

On the whole, our experiences make it seem unlikely that the level of the oestrogenic hormones plays any considerable rôle in the clinical effect provoked by endocrine therapy in metastasizing mammary cancer. However, in this connection some recent studies concerning the relation between the oestrogenic hormone effect and certain enzymes connected with tumour growth are interesting (TALALAY *et al.* 1958, ENGEL 1958).

The influence on the clinical result of the localization of the metastases has been extensively considered previously (TAYLOR 1956, KENNEDY 1958, HORTLING *et al.* 1958, 1961, American Subcommittee on Breast and Genital Cancer 1960, LUFT 1960, and others). Metastases

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CONCLUSIONS

The observations made in this study seem to favour a certain scheme for the handling of a patient showing signs of disseminated spread from a mammary cancer In patients of premenopausal age, castration, perhaps in rapidly progressing cases combined with cortisone in doses that suppress the adrenal cortex, is preferable as the first treatment. When this therapy is ineffective, or if a favourable effect has receded the next step should be norandrostenolone phenylpropionate or decanoate, or perhaps some other anabolic preparation with insignificant virilizing properties, or cortisone, if it has not already been used simultaneously with castration. Hypophysectomy should be the last resort. Postmenopausally especially in patients more than 55 years of age, the treatment of choice should probably be oestrogens in large doses, nortestosterone preparations the second step and hypophysectomy the last measure. Castration can be tried on patients of an early postmenopausal age, and cortisone at all ages as an intermediate treatment. The traditional androgen therapy is, on the whole, not indicated. It is not intended that this scheme of treatment should interfere with the traditional radiological therapy

SUMMARY

888 endocrine treatment courses were given to 375 patients suffering from metastasizing mammary cancer in an advancing stage. The uniformly evaluated clinical results were classified as favourable when objective signs of remission or arrest of the disease were observed, but subjective improvement was not evaluated. The frequency and duration of a favourable response to treatment were considered, special stress being placed on the order in which the endocrine manoeuvres had been administered. (Cf. Fig. 1 in which the number of patients in the different groups is also seen).

Castration, mostly performed by radiological means, had a favourable effect in 27.4 per cent of the cases, lasting 25 months on an average when performed as the first manoeuvre, but only in 10 per cent when performed as the second.

As the first treatment course, testosterone preparations had a favourable effect in 25.6 per cent of the cases treated lasting 11.7 months on an average, and as the second course in 10.3 per cent. The side effects were considerable.

As the first treatment, oestrogenic hormones given in the late postmenopausal period induced a favourable response in 26.5 per cent of the cases treated lasting on an a verage 15 months.

Cortisone used in doses sufficient to depress the function of the adrenal cortex induced a favourable clinical response in 7.7 per cent when used as the first manoeuvre, in 13.6 per cent as the second and in 21 per cent as the third. The effect induced lasted for a shorter time than after other forms of endocrine treatment.

Norandrostenolone phenylpropionate, with clearly less disturbing androgenic properties than the testosterone preparations, induced a favourable clinical response in 30.3 per cent, lasting on an average 12.3 months when given as the first manoeuvre, in 21.4 per cent as the second, in 18.6 per cent as third and in 40 per cent when administered as the fourth therapeutic procedure. The corresponding precentages for nor androstenolone decanoate were 37.5 per cent as first manoeuvre and 32.1 per cent on an average as 2nd — 4th manoeuvre.

The results with hypophysectomy were favourable responses in 50 per cent as first manoeuvre, 37.5 per cent as second, 25 as third or fourth and 40 as fifth therapeutic manoeuvre. The duration of the clinical response on an average was more than 21 months as first manoeuvre, and more than 19 months as later treat ment.

The survival time from the onset of

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metastases was on an average 28.3 months when one favourable response was recorded with some of the endocrine measures used 50 1 months when 2 or more favourable responses were recorded and 14 1 months when the clinical effect was poor In a control series of 121 patients that did not receive endocrine treatment at all, but roentgen treatment in about the same quantity as the endocrinologically treated patients received the survival time was 14.8 months on an average. These figures indicated that endocrine therapy when inducing a favourable clinical response, does actually prolong the life of the patient.

In the material, the effect of roentgen treatment and of various simultaneously given endocrine treatments, the correlation between variations in the oestrogenic effect in the vaginal smear and the clinical effect as well as the age factor were also considered in certain groups. The chances of a patient responding favourably to endocrine therapy were found to be no greater when he had once or even twice before responded well to another such therapy

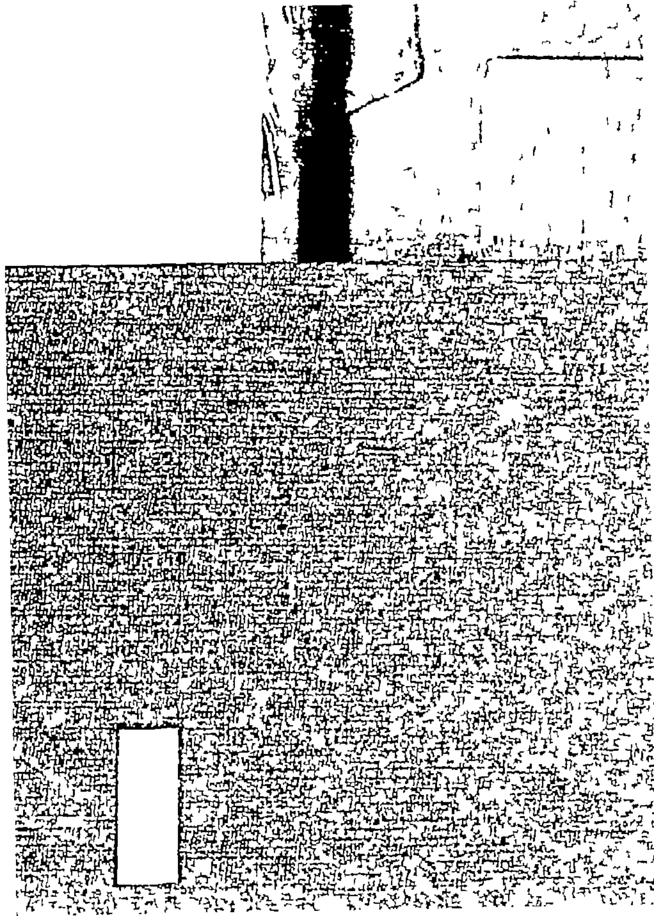
On the basis of the results observed a general scheme is suggested for the endocrine treatment of metastasizing mammary cancer Testosterone preparations no longer have any place in this therapy

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A COMPARATIVE STUDY OF RESPIRATORY DISEASE IN ENGLAND & WALES AND NORWAY

BY

TORBJÖRN MORK

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A Comparative Study of

Respiratory Disease

in England & Wales and Norway

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE
DEPARTMENT OF MEDICAL STATISTICS AND EPIDEMIOLOGY
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TORBJÖRN MORK, M.D., Ph. D

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INTRODUCTION

The mass-disease problems of the economically advanced countries have altered much since the beginning of this century In 1900 the infectious diseases were the main public health problem. At present the more chronic non-infectious diseases, as measured in terms of disability and death, are of major importance. The result of this changing situation is an established and increasing trend among workers in the field of preventive medicine to accord greater emphasis to diseases characteristic of middle and old age. This trend is reflected also in the field of epidemiology and the application of epidemiological methods has been a very profitable approach to the solution of various problems concerning the distribution and etiology of chronic diseases.

One of the most striking features in the epidemiology of chronic diseases is the big difference between advanced countries in the importance of cardio-respiratory diseases in general, and chronic bronchitis in particular as recorded causes of death. According to the official mortality statistics, chronic bronchitis in England & Wales ranks third as a cause of death in middle-aged males, and first as a cause of disability in the working population over 40 years of age (Jones 1959). In most other countries chronic bronchitis as a recorded cause of death is of very little importance, except in the very old. It is therefore not surprising that British workers in the last decade have investigated various aspects of this disease entity Many of these authors (Reid 1956, Ogilvie & Newell 1957 Stuart Harris & Hanley 1957) have drawn attention to the tremendous difference in bronchitis death-rates between England & Wales and other countries, and emphasized the need for international comparative studies. Few such studies, however have so far been carried out.

Recently a study group convened by The Council for International Organizations of Medical Sciences under the joint auspices of UNESCO and WHO (1959) listed chronic bronchitis (Chronic cardiopulmonary insufficiency) as one of the conditions specially suitable for comparative international studies, on the ground that it was a common condition of wide distribution, the etiology of which was obscure. The interest in comparative international studies in this field reflects the uncertainties involved in direct comparisons of published mortality and morbidity data from different countries. Are differences as observed from available vital statistics *real* in the sense that they measure actual differences in the prevalence of disease and the number of deaths? Do disparities also exist in the prevalence of early disease symptoms? Finally can observed differences, if real, be explained by variations in the exposure to environmental factors that might be of importance in the causation of the disease?

Some of these investigations will be discussed more closely in later sections of this paper. The main results can be briefly summarized as follows:

The mortality from chronic bronchitis shows great geographical variations between and within countries. There is an excess mortality in urban compared with rural areas, and a marked social gradient with highest mortality in the lower social classes. The male/female ratio is high, particularly between the ages of 40 and 64. The morbidity shows the same pattern, but less markedly. Most studies strongly suggest that atmospheric pollution and cigarette-smoking may be causative or contributive factors in the evolution of the disease.

Definition of chronic bronchitis

The limited understanding of this disease entity prior to the last few years may account for the fact that as yet no internationally accepted precise clinical definition has been established. The study group convened by The Council for International Organizations of Medical Sciences (1959) proposed the following definition: 'Chronic bronchitis may be defined as a disease which

a) is characterized by chronic and persistent cough,

b) is punctuated by annual or seasonal exacerbations,

c) is associated with the production of purulent sputum,

d) leads to increasing breathlessness and disability

e) commonly ends in death by congestive heart failure.

Unfortunately neither this nor other symptomatic definitions suggested recently (Fletcher *et al* 1959 Report of a Ciba Guest Symposium 1959) exclude other conditions which may produce similar symptoms, and the statement by Stuart Harris & Hanley (1957) that no one has yet evolved a definition of chronic bronchitis which avoids the need to exclude other chronic pulmonary diseases' still holds. These difficulties regarding definition and terminology do not, however invalidate comparative epidemiological studies, but necessitate certain precautions. In field-surveys one will have to compare the prevalence of symptoms and objective measurements, rather than the prevalence of cases given a certain diagnostic label. Fletcher *et al.* (1959), in an attempt to compare the prevalence of chronic bronchitis in London postmen with that found in three groups of males in the U.S.A. by Pemberton (1956), observed that by using three different definitions of chronic bronchitis, which were all compatible with Pemberton's words, the prevalence of the disease in the postmen could appear greater than in the American coalminers, or the same as in the American rural population.

In comparative analyses of available vital statistics data, one may have to use rather broad working definitions' like the one given by Reid (1956): 'That condition which is described as chronic bronchitis by general practitioners when they complete certificates of cause of incapacity or death

The answers to such questions may establish conclusively whether or not a problem really exists and may give suggestions on etiological factors, thus providing a better basis for the application of suitable preventive measures.

This study was designed to try to elucidate these problems through a critical analysis of existing statistical data, and through field-surveys in comparable population samples in countries with contrasting mortality In the greater part of the study emphasis has been laid on chronic bronchitis' rather than on the total group of cardio-respiratory diseases, as observed differences in mortality between countries are most striking in this subgroup The field-surveys have been carried out in England and Norway the countries with highest and lowest recorded mortality from chronic bronchitis in middle-aged persons, and emphasis has also been laid on these countries in the analysis of existing statistical data.

The first clinical description of chronic bronchitis as a disease entity is usually ascribed to Badham who published his classic paper on this condition in 1808. The first attempt to use vital statistics in assessing the prevalence and mortality of the disease, is according to Medvei (1957) found in an essay published by Buxton in 1810 The history of bronchitis can, however be traced back through the centuries. The first description quoted by Sigerist (1951) is from an Assyrian tablet published by Labat & Tournay (1945) If the patient suffers from hissing cough if his wind pipe is full of murmurs, if he has coughing fits, if he has phlegm,

Apart from the recognition of the relation of chronic bronchitis to emphysema and heart failure, little advance was made in the understanding of the nature of this disease in the years between Badham s paper and the end of World War II According to Ogilvie & Newell (1957) the tendency was to regard the disease as degenerative, and as part of the process of ageing. During the past ten years, however this situation has been transformed by a number of studies. The morbid anatomy of the respiratory tract in chronic bronchitis has been studied by McA. Reid (1954 1956) May (1954) Mulder et al. (1952) Mulder & Hers (1955) Elmes et al (1953 1957 1959) have investigated the bacteriology of the sputum in patients with chronic bronchitis, and works by Oswald et al (1953), Stuart Harris & Hanley (1957) and Fletcher et al. (1959) have added to our knowledge of the clinical picture of this disease entity A comprehensive survey of the main results of investigations carried out previous to 1956 is given in the monograph by Stuart Harris & Hanley (1957) The epidemiology of chronic bronchitis has been studied by numerous workers. Three different types of data have provided the basic material for most of these studies:

a) Vital statistics on morbidity and mortality
b) Anamnestic and clinical data on hospital patients and on samples of 'healthy' populations surveyed.
c) Quantitative data on various environmental factors.

Some of these investigations will be discussed more closely in later sections of this paper The main results can be briefly summarized as follows:

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I

Examination of Available Statistical Data

ON THE VALIDITY OF INTERNATIONAL COMPARISONS OF VITAL STATISTICS

Mortality statistics

The use of mortality statistics in international comparisons is subject to many limitations because of a lack in uniformity due to various causes. The main sources of variations are (WHO 1957)

a) Standards of medical practice.
b) Criteria on which cause of death is assigned.
c) Proportions of autopsies practised.
d) Cultural or psychological reasons for incomplete or faulty notification of certain forms of death in many countries.
e) Practice in vital statistics services.

Some of these sources of variation may be present even within the same country at the same time, as shown by Fonseka (1958) in his analysis of certification habits among British general practitioners. Most of the factors listed above are unfortunately not measurable, and it is therefore impossible to make appropriate allowances for them in comparative studies of mortality statistics from different geographical or administrative areas. It seems very difficult to assess with any degree of accuracy the possible influence on recorded mortality rates of differences in the qualifications of physicians, and in the various types of medical facilities available in different countries. Further there is the problem of divided medical opinion on the relationship between particular syndromes and/or diseases. The two relevant statistical factors the classification used in putting the large number of diseases into relatively few groups for purposes of tabulation and the method of selecting the cause of death to be tabulated when more diseases than one are entered on the death certificate, are now at least in theory standardized. The International Statistical Classification of Diseases, Injuries, and Causes of Death (WHO 1948) has been almost universally adopted In some countries, however special arbitrary rules are still applied in selecting cause of death for tabulation when certain combinations of diagnoses appear on the death certificate, for example in Denmark, where chronic bronchitis is

entered on the death certificate together with various other respiratory and/or cardiovascular diseases (Christensen & Wood 1958).

According to the rules laid down in the International Statistical Classification, the causes selected for primary tabulation should be the underlying cause of death defined as the disease or injury which initiated the train of morbid events leading directly to death. The responsibility for indicating the underlying cause of death was placed on the certifying physician, who was regarded to be "in a better position than any other individual to decide which of the morbid conditions led directly to death and to state the antecedent conditions, if any which gave rise to this cause" (WHO 1948). This procedure increases the importance of the medical factors of variation compared with the statistical ones, as the mortality statistics must reflect the average clinical opinion of the certifiers. A further complication may arise from an incomplete understanding by certifiers of the underlying cause of death concept. According to Moriyama (1956) some consider it to be the terminal disease or condition responsible for death, whereas others think it is the principal disease under treatment. It has been reported that in 20–25 % of death certificates, the certifiers opinion of the underlying cause of death is not clear (Committee on Medical Certification of Causes of Death 1958).

The validity of the underlying cause of death as a measurement of mortality remains doubtful, even if these differences in the certifiers' interpretations of the concept could be eliminated. Particularly in the case of elderly persons, the doctor is faced with the nearly impossible task of singling out the sequence of related diseases and conditions from the complex of symptoms present in the terminal stages of more chronic conditions, for example within the large group of cardiovascular respiratory diseases. One may suspect that in many instances the selection of a single cause within the larger group takes place more or less at random. This factor seems of great importance in a chronic, long-standing disease of obscure etiology like chronic bronchitis.

Some improvement in the accuracy of mortality statistics might be obtained by multiple cause tabulation. As pointed out by the Committee on Medical Certification of Causes of Death (1958) this will raise numerous methodological problems. This is probably the reason why most countries do not publish statistics on multiple causes of death, not even to a limited extent.

The same factors still more seriously handicap an analysis of the time trend in mortality by cause in different countries. Since the beginning of this century six different lists of classification have been brought into use in most countries, and prior to the last decade the various national statistical offices followed different criteria in assigning some of the causes of death stated in the medical certificates to the rubrics of those classification lists (Pascua 1951). It has been observed (WHO 1952) that changes in rules for selecting cause of death for tabulation may produce fictitious trends in mortality rates. For example, the

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bidity is relative, and no satisfactory definition of sickness has been agreed upon. These difficulties regarding definition were stressed by Stocks (1949) who said, the distinction between living and dead is clear cut, but no such frontier line between sickness and health can be said to exist except in the case of acute illness caused immediately and directly by an external agent. There is a zone between the two states in which the division whether the subject is sick or not depends on definitions of standards of good health, and also on who decides. It is often said that only a physician is competent to decide what a patient is suffering from, but the patient often has to decide whether or not he is ill at all. In these circumstances it seems necessary for practical purposes to adopt a more selective concept of sickness which might be suitable for objective recording. In most studies, therefore, absence from work or inability to participate in the daily activities normally undertaken, has been taken as an indication of sickness.

Morbidity statistics for the total population are not published in any country. Some countries, however, publish claims on health insurance schemes of various types, covering parts of the population. The most comprehensive statistics of this type refer to the total working population, and give data for certified sickness absence. The comparability of these data is, however, very restricted, even within the same country. As emphasized by Benjamin (1959) sickness absence will depend not only on the degree of incapacity but also on whether there is any loss of income involved. This factor may vary considerably from one health insurance scheme to another and produce fictitious differences in morbidity, particularly from minor illnesses. Fletcher (1959) in a study of bronchitis morbidity in transport workers and post-office workers in London, found a much lower morbidity in the transport workers than in the Post Office group. The latter had their full salary paid during certified sickness absences, whereas the former group did not get sick pay from the employer causing a substantial decrease in income during periods of absence.

Regarding the recorded cause of sickness absence, this may be inaccurate for various reasons apart from the medical ones. Any individual may have several diseases at the same time, and there are no universally adopted rules for selecting one diagnosis to be recorded. Furthermore, the need to submit the medical certificate to any employer may tend to make the certifier circumspect in his description of the condition causing incapacity. He may, for instance, consider it necessary to conceal a condition which is likely to jeopardize the continued employment of the patient.

These limiting factors apply to the comparability of sickness absence statistics in the total working population as well as in the different occupational groups. Comparisons between occupations are further restricted by *differences* in the nature of work done, the environment in which it is performed, and other conditions of employment. These factors may vary widely even within the same broad occupational group in different areas, and may probably to a considerable

mortality from diabetes in 1949 was reduced by 45 % in Canada and 43 % in the U.S.A., when selection according to the certifiers statement was compared with selection according to the arbitrary rules used previously

In order to preserve, as far as possible, the continuity of mortality rates by cause and age, it has been recommended (WHO 1948) that comparability factors should be calculated when changes in classification rules are adopted. Unfortunately, however few countries have prepared or published such data.

The time trend in mortality by cause will also be influenced by increasing medical knowledge and better diagnostic and therapeutic facilities. The concept of many diseases changes, and the diagnoses become more accurate. In addition, from time to time medical opinion is influenced by particular attention given to certain conditions, and excessive reporting in such a direction may result.

Hill (1955) has emphasized that in making comparisons between death rates from different causes of death at different times or between one country and another it must be realized that one is dealing with material which is, in Raymond Pearl's words, fundamentally of a dubious character' Despite all such qualifications, mortality statistics remain one of the most important sources of epidemiological data. The heterogeneity of the data necessitates great caution in drawing conclusions from minor numerical differences. Major disparities and well-marked trends will, however generally suggest that the observed differences possess a definite meaning and might be invested with an inferential value.

Morbidity statistics

Mortality statistics unfortunately can not provide a comprehensive picture of morbidity Only for inevitably fatal diseases will mortality data give an accurate picture of their distribution and relative importance. In diseases with a low fatality rate, however such data are without validity as measurements of disease incidence and/or prevalence. Consequently in order to get some indication of morbidity from diseases where fatality varies, one has to study statistics on morbidity

Morbidity data may be obtained from many sources· the most important of these are·

a) Records of health insurance and/or social security schemes

b) Records of sickness absence from school or place of work.

c) Hospital records.

d) General practitioners' records.

e) Morbidity surveys in the general population.

There are many difficulties in using such data for comparative purposes, whatever sources they are obtained from. While death is unconditional, mor

bidity is relative, and no satisfactory definition of sickness has been agreed upon. These difficulties regarding definition were stressed by Stocks (1949) who said: the distinction between living and dead is clear cut, but no such frontier line between sickness and health can be said to exist except in the case of acute illness caused immediately and directly by an external agent. There is a zone between the two states in which the division whether the subject is sick or not depends on definitions of standards of good health, and also on who decides. It is often said that only a physician is competent to decide what a patient is suffering from, but the patient often has to decide whether or not he is ill at all. In these circumstances it seems necessary for practical purposes to adopt a more selective concept of sickness which might be suitable for objective recording. In most studies, therefore, absence from work or inability to participate in the daily activities normally undertaken, has been taken as an indication of sickness.

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extent influence the sickness absence rates. In comparing occupational groups in different countries, one will also have to consider the possible effect of differences in the selection of people to various occupations

Morbidity statistics based on hospital data are not available on a national scale in most countries. Statistics may be obtained however from selected hospitals or groups of hospitals in some areas, but the validity of such data for comparative studies of disease incidence and/or prevalence is dubious. Firstly various selection factors are operating determining the admission of cases to any particular hospital or groups of hospitals in any country Secondly what may be regarded in one area as sufficient incapacity to justify admission to hospital, may be regarded differently in another milieu due to various cultural, social and economic factors.

General practitioners records seem likewise of little value for comparative studies. They are not usually compiled for statistical purposes, and in many cases at least are probably not very complete, or accurate. Furthermore, it is usually impossible in both hospital data and data from general practitioners to obtain an accurate estimate of the population the cases refer to and rates cannot therefore be calculated.

The general restrictions on the use of existing vital statistics for comparative purposes outlined in this section, have to be kept in mind for all types of comparative investigations based on such data. They provide the background for the more detailed discussions in the following sections on the validity of the particular comparisons made in the present study

PREVIOUS INVESTIGATIONS

Only two critical studies of differences between countries in recorded mortality from chronic respiratory diseases are known to the author Karvonen & Kihlberg (1957) studied bronchitis, pneumonia and heart diseases as causes of death in England & Wales and Finland. Their study is based on available mortality statistics from the two countries. The recorded mortality from chronic bronchitis in England & Wales is about 50 times as high as in Finland, nevertheless, the total mortality in Finland exceeds that of England & Wales in all age-groups. There was no consistent difference in pneumonia mortality between the two countries, but the mortality from arteriosclerotic and degenerative heart disease was found markedly higher in Finland than in England & Wales. The difference was larger in men than in women The over all mortality from bronchitis, pneumonia and arteriosclerotic and degenerative heart disease was higher in Finland than in England & Wales. After having discussed various possibilities of diagnostic transfers, they conclude that the differences in mortality cannot be fully

explained by a possible diagnostic or real transfer in Finland of deaths from bronchitis under the heading of heart disease

Christensen & Wood (1958) investigated the recorded bronchitis mortality in Denmark compared with that in England & Wales. They found a fifteenfold excess mortality from bronchitis in England & Wales, and only half this excess mortality could possibly be accounted for by differences in classification. The mortality from all other respiratory conditions and for all cardiac conditions except the group Other and unspecified disease of heart' (International Statistical Classification, Detailed List, No. 434) was found higher in England & Wales than in Denmark, and the mortality from most other diseases showed a marked similarity Some causes of this excess were considered. The cigarette consumption of England & Wales was twice that of Denmark, and in the authors' view this may contribute to the excess mortality whereas the differences in the age distribution of the populations, social class, climate and atmospheric pollution of the two countries did not appear to be important factors when considered separately They conclude: 'Within the strict limits imposed by differences in method of compiling the death rates, it would appear that there is a real excess of disease labelled bronchitis in England & Wales compared with Denmark.

In both these studies it is concluded that the confirmation of the supposed real differences in mortality and the elucidation of its causes are only likely to result from comparative field-surveys in the different countries.

OWN INVESTIGATIONS

This study is restricted to the 40-64-year age-group. This age-group was decided upon after a preliminary review of the literature on chronic cardio-pulmonary diseases revealed that these disease entities are of relatively little importance under the age of 40 as a cause of either incapacity or death. The validity of comparing death rates by cause in persons over 64 years of age seems dubious. Firstly the accuracy of diagnoses probably decreases with age, mainly due to the fact that in old persons numerous diseases often coincide. Secondly the rates for some diseases, in the older age-groups, may conceivably be influenced by competition of various causes of death associated in one way or another with common factors. If one or more of these diseases have a substantial mortality it may tend to deplete the number of persons susceptible to other diseases associated with the same factors. In other words, the fraction of the cohort most likely to develop a particular disease is selectively drained by other causes of death as well, and thus may cause a depression of certain cause-specific rates in the older age-groups. This factor may be of importance in the disease entity under study in which one of the presumptive etiologic factors (cigarette-smoking) has, in recent studies, (Doll & Hill 1956, Hammond & Horn 1958) been

extent influence the sickness absence rates. In comparing occupational groups in different countries, one will also have to consider the possible effect of differences in the selection of people to various occupations.

Morbidity statistics based on hospital data are not available on a national scale in most countries. Statistics may be obtained, however from selected hospitals or groups of hospitals in some areas, but the validity of such data for comparative studies of disease incidence and/or prevalence is dubious. Firstly various selection factors are operating determining the admission of cases to any particular hospital or groups of hospitals in any country. Secondly, what may be regarded in one area as sufficient incapacity to justify admission to hospital, may be regarded differently in another milieu due to various cultural, social and economic factors.

General practitioners records seem likewise of little value for comparative studies. They are not usually compiled for statistical purposes, and in many cases at least are probably not very complete, or accurate. Furthermore, it is usually impossible in both hospital data and data from general practitioners to obtain an accurate estimate of the population the cases refer to, and rates cannot therefore be calculated.

The general restrictions on the use of existing vital statistics for comparative purposes outlined in this section, have to be kept in mind for all types of comparative investigations based on such data. They provide the background for the more detailed discussions in the following sections on the validity of the particular comparisons made in the present study

PREVIOUS INVESTIGATIONS

Only two critical studies of differences between countries in recorded mortality from chronic respiratory diseases are known to the author. Karvonen & Kihlberg (1957) studied bronchitis, pneumonia and heart diseases as causes of death in England & Wales and Finland. Their study is based on available mortality statistics from the two countries. The recorded mortality from chronic bronchitis in England & Wales is about 50 times as high as in Finland, nevertheless, the total mortality in Finland exceeds that of England & Wales in all age-groups. There was no consistent difference in pneumonia mortality between the two countries, but the mortality from arteriosclerotic and degenerative heart disease was found markedly higher in Finland than in England & Wales. The difference was larger in men than in women. The over all mortality from bronchitis, pneumonia and arteriosclerotic and degenerative heart disease was higher in Finland than in England & Wales. After having discussed various possibilities of diagnostic transfers, they conclude that the differences in mortality cannot be fully

TABLE 1

MORTALITY 1955

Rates per 100,000 per year 40-64 years. Age-standardized

MALES

	Pneumonia and bronchitis	Tuberculosis of respiratory system	Total cardio-vascular	Arteriosclerotic and degenerative heart disease	Other diseases of heart	Malignant neoplasms of respiratory system	All other cancers	Senility ill-defined and unknown causes	All diseases
Austria	23.9	61.3	364.1	183.9	40.0	102.9	194.0	24.3	982.8
Belgium	45.9	69.2	402.4	177.1	78.8	76.2	170.2	45.0	1032.3
Canada	19.9	17.9	531.2	394.2	14.3	48.1	133.1	5.1	918.6
Denmark	10.6	8.2	323.1	197.2	41.0	56.2	158.6	3.1	684.5
Finland	39.1	128.8	664.6	432.6	47.1	113.2	213.3	6.0	1324.0
France	22.0	81.3	311.0	71.1	102.1	60.5	178.9	110.0	1060.6
Italy	42.8	59.6	323.6	155.2	21.5	55.6	172.1		
Netherlands	27.6	12.6	237.5	170.5	15.6	78.8	148.6	41.7	700.8
New Zealand	28.9	23.3	479.2	338.8	22.0	61.5	150.9	1.2	875.5
Norway	10.3	27.4	280.7	167.8	21.3	22.8	166.2	31.4	645.2
Sweden	17.0	19.4	322.2	185.5	24.7	27.2	135.1	6.8	655.9
Switzerland	17.1	33.4	328.7	179.3	28.4	70.6	184.3	2.0	833.5
England & Wales	116.7	34.5	447.9	276.6	14.2	150.9	160.3	0.8	1042.2
U.S.A. (White)	20.9	19.7	635.7	466.3	17.0	63.6	155.2	14.3	1073.6

Calculated from Annual Epidemiological and Vital Statistics, WHO, Geneva 1958

shown to be associated with a number of other diseases. It seems nearly impossible to assess quantitatively with any degree of accuracy the possible effect of this competition in view of the present limited knowledge of the multiple factors involved in the causation of most chronic diseases.

Mortality international comparisons

Tables 1 and 2 give the death rates in 1955 from certain important causes in 14 economically advanced countries. The rates are standardized for age on the estimated England & Wales population on 1 January 1955 The data are obtained from WHO Annual Epidemiological and Vital Statistics 1955 (1958) The 14 countries were selected on the following bases:

1 Mortality rates by age, sex and cause were available.
2. Data on certain environmental factors which may be related to the diseases under study exist for these countries.
3 There are no major racial differences between the populations.
4 Standard of medical care and vital statistics were assumed to be sufficiently similar to justify comparisons.

In the tables diagnostic group 31 (Pneumonia) and 32 (Bronchitis) in the abbreviated B-list of the International Statistical Classification of Diseases, Injuries, and Causes of Death (WHO 1948) are pooled. This is done partly because the number of deaths in each of these groups in many of the countries is very small, and thus subject to large sampling variation and partly because one may suspect that transfers from one of these groups to the other frequently take place due to different medical traditions. It is found that the male death rates in this combined group (Pneumonia and bronchitis) in England & Wales are more than twice as high as those in any of the other countries, five times as high as that of the white population in the U.S.A. and more than ten times the rates of Denmark and Norway The female rates show the same tendency if less pronounced.

Clinical tradition, certification habits and classification rules might have caused transfers of deaths from this group to other groups of cardiac and pulmonary diseases, or to group B 45 (Senility without mention of psychosis, ill-defined and unknown causes) It will be seen from the tables that the rates from all these causes vary considerably particularly for B 26 (Arteriosclerotic and degenerative heart disease), 160-5 (Cancer of the respiratory system) and B 45 This in contrast to the rates for malignant neoplasms excluding respiratory cancer which are rather similar

Theoretically transfers between groups of related diseases could account for the observed differences in bronchitis-pneumonia rates between England & Wales and some other countries (U.S.A. and Finland) which have higher rates from cardiovascular diseases. This possibility was, as mentioned previously carefully

TABLE 1

MORTALITY 1955

Rates per 100,000 per year 40-64 years. Age-standardized

MALES

	Pneumonia and bronchitis	Tuberculosis of respiratory system	Total cardio-vascular	Arteriosclerotic and degenerative heart disease	Other diseases of heart	Malignant neoplasm of respiratory system	All other cancers	Senility ill-defined and unknown causes	All diseases
Austria	23.9	61.3	364.1	183.9	40.0	102.9	194.0	24.3	982.8
Belgium	43.9	69.2	402.4	177.1	78.8	76.2	170.2	45.0	1032.3
Canada	19.9	17.9	531.2	394.2	14.3	48.1	155.1	5.1	918.6
Denmark	10.6	8.2	323.1	197.2	41.0	56.2	158.6	5.1	684.5
Finland	39.1	128.8	644.6	432.6	47.1	113.2	213.3	6.0	1324.0
France	22.0	81.3	311.0	71.1	102.1	60.5	178.9	110.0	1060.6
Italy	42.8	59.6	323.6	155.2	21.5	55.6	172.1		
Netherlands	27.6	12.6	257.5	170.3	15.6	78.8	148.6	41.7	700.8
New Zealand	28.9	23.3	479.2	338.8	22.0	61.5	150.9	1.2	875.5
Norway	10.3	27.4	280.7	167.8	21.3	22.8	164.2	31.4	645.2
Sweden	17.0	19.4	322.2	189.3	24.7	27.2	135.1	6.8	655.9
Switzerland	17.1	33.4	328.7	179.3	28.4	70.6	184.3	2.0	853.5
England & Wales	116.7	34.5	447.9	276.6	14.2	130.9	160.3	0.8	1042.2
U.S.A. (White)	20.9	19.7	635.7	466.3	17.0	63.6	155.2	14.5	1073.6

Calculated from: Annual Epidemiological and Vital Statistics, WHO, Geneva 1958

TABLE 2

MORTALITY 1955

Rates per 100,000 per year 40-64 years. Age-standardized

FEMALES

	Pneumonia and bronchitis	Tuberculosis of respiratory system	Total cardio-vascular	Arteriosclerotic and degenerative heart disease	Other diseases of heart	Malignant neoplasm of respiratory system	All other cancers	Senility ill-defined and unknown causes	All diseases
Austria	11.8	15.5	222.0	70.8	25 9	10.7	225.5	9 4	644.2
Belgi m	9 1	11.9	228.8	64 1	48.6	8.8	211.9	23.0	625 9
Canada	9.7	7 9	268.0	127.2	9.7	9.6	207.8	2.6	605.6
Denmark	8.5	5.6	183.0	66.1	19.5	9.8	272.9	1.8	572.9
Finland	16.9	29.6	329.3	121.3	26.5	12.8	184 1	3.6	692.4
France	9.7	18.6	186.2	22.2	61.6	8 4	179.5	59.5	630.5
Italy	19.6	13.8	243.7	85 1	19.2	9 1	178.3	12.3	521 4
Netherlands	9.8	5.1	161.7	64.0	11.0	6.2	206.1		
New Zealand	10.4	10.7	277.2	104.5	12.9	7.0	203.8	0.4	618.1
Norway	9.5	10.1	162.2	50.4	13.8	7.5	194.8	12.1	470.1
Sweden	12.8	8.0	217.7	72.6	20.4	7 9	197.7	4.6	555.1
Sw tzerland	7 9	15.0	223.0	84 9	14 9	7 1	208 4	2.6	598.2
England & Wales	34.2	8.9	231.6	85.6	9 4	17.2	206.7	0.3	621.3
U.S.A. (White)	9.3	5.0	271.6	136.9	7 1	8.9	207.6	5.2	611.6

Calculated from Annual Epidemiological and Vital Statistics, WHO Geneva 1958

studied by Karvonen & Kihlberg (1957) for the difference between England & Wales and Finland, but rejected as a probable explanation of the total difference in bronchitis mortality. The majority of countries, however, have lower rates than England & Wales from cardiovascular diseases and also lower rates for total disease mortality. This is most pronounced for Sweden, Denmark and Norway, as will be seen from Table 3, which gives death-rates from a cardio-respiratory group (B 1, 26, 27, 31, 32, and 160-5) including B 45, rates from all

TABLE 3

MORTALITY 1955

Rates per 100,000 per year 40-64 years. Age-standardized

	MALES			*FEMALES*		
	Cardio-resp.	All other diseases	All diseases	Cardio-resp.	All other diseases	All diseases
Austria	436.3	546.5	982.8	144.1	500.1	644.2
Belgium	492.2	540.1	1032.3	165.5	460.4	625.9
Canada	499.5	419.1	918.6	166.7	438.9	605.6
Denmark	318.3	366.2	684.5	111.3	461.6	572.9
Finland	766.8	557.2	1324.0	210.7	481.7	692.4
France	447.1	613.5	1060.6	180.0	450.5	630.5
Netherlands	346.8	354.0	700.8	108.4	413.0	521.4
New Zealand	475.7	399.8	875.5	145.9	472.2	618.1
Norway	281.0	364.2	645.2	103.4	366.7	470.1
Sweden	284.4	371.5	655.9	126.3	428.8	555.1
Switzerland	330.8	322.7	653.5	132.4	465.8	598.2
England & Wales	573.7	468.5	1042.2	155.6	465.7	621.3
U.S.A. (White)	602.0	471.6	1073.6	172.4	439.2	611.6

other diseases, and total disease mortality. The excess in total disease mortality in both sexes in England & Wales compared with the Scandinavian countries, is caused by a higher mortality from diseases in the cardio-respiratory group as well as from other diseases. The disparity is most pronounced for males in the former disease group. The question of whether the observed differences in death-rates in the more specific groups of cardiac and respiratory diseases are real or caused by transfers between the groups, cannot be answered on the basis of the given data. It seems necessary to carry out comparative studies of certification and classification habits in the different countries to elucidate this problem.

Table 4 shows the male/female ratios for the same disease groups in the same countries. In all groups of cardiac and respiratory diseases males have an excess mortality. This is particularly pronounced for the groups 160-5, B 26 and B

TABLE 2

MORTALITY 1955

Rates per 100,000 per year 40-64 years. Age-standardized

FEMALES

	Pneumonia and bronchitis	Tuberculosis of respiratory system	Total cardio-vascular	Arteriosclerotic and degenerative heart disease	Other diseases of heart	Malignant neoplasm of respiratory system	All other cancers	Senility ill-defined and unknown causes	All diseases
Austria	11.8	15.5	222.0	70.8	25.9	10.7	225.5	9.4	644.2
Belgium	9.1	11.9	228.8	64.1	48.6	8.8	211.9	23.0	625.9
Canada	9.7	7.9	268.0	127.2	9.7	9.6	207.8	2.6	605.6
Denmark	8.5	5.6	183.0	66.1	19.5	9.8	272.9	1.8	572.9
Finland	16.9	29.6	329.3	121.3	26.5	12.8	184.1	3.6	692.4
France	9.7	18.6	186.2	22.2	61.6	8.4	179.5	59.5	630.5
Italy	*19.6*	*13.8*	*243.7*	*85.1*	*19.2*	9.1	178.3		
Netherlands	9.8	5.1	161.7	64.0	11.0	6.2	206.1	12.3	521.4
New Zealand	10.4	10.7	277.2	104.5	12.9	7.0	203.8	0.4	618.1
Norway	9.5	10.1	162.2	50.4	13.8	7.5	194.8	12.1	470.1
Sweden	12.8	8.0	217.7	72.6	20.4	7.9	197.7	4.6	555.1
Switzerland	7.9	15.0	223.0	84.9	14.9	7.1	208.4	2.6	598.2
England & Wales	34.2	8.9	251.6	85.6	9.4	17.2	206.7	0.3	621.3
U.S.A. (White)	9.3	5.0	271.6	136.9	7.1	8.9	207.6	5.2	611.6

Calculated from *Annual Epidemiological and Vital Statistics*, WHO Geneva 1958

31 32. The group 'Malignant neoplasms excluding 160-5' shows a slight female excess in most countries. Dividing the total disease mortality into a 'Cardio-respiratory group' and a group of 'All other diseases' one finds that in the latter group the death experience is remarkably similar in the two sexes in most countries. The higher male rates from 'All diseases' are almost entirely due to excess cardio-respiratory mortality

The differences between countries in death-rates from B 31+32 are usually in the same direction in the two sexes. The rank correlation coefficient between male and female rates in the 14 countries is statistically significant (r = 0.462, P = 0.0244) The male/female ratios are closely correlated to the male death-rates (r = 0.6956, P = 0.0009), but not significantly correlated to the female death-rates (r = 0.1284 P = 0.5412). In other words, the inter-country differences in mortality *are considerably more* pronounced in the males than in the females. The significance of this feature will be discussed in the section on environmental factors.

Mortality in England & Wales and Norway

The comparisons made above give strong support to the hypothesis that substantial *real international differences* exist in mortality from cardio-respiratory diseases in general, and probably also from bronchitis and pneumonia. It might be useful, however to study in some more detail the mortality statistics of the two countries, i. e. England & Wales and Norway showing the extreme values in death-rates from these diseases.

Age- and sex specific rates have been calculated for 5-year groups between 40 and 64 years of age. The rates were calculated as averages for the period 1951 5 to reduce a possible effect of influenza epidemics on one-year respiratory rates, and also because of small numbers of deaths per year in some of the groups. Both countries have in the period under study followed the rules for certification and classification of causes of death laid down in the International Statistical Classification of Diseases, Injuries, and Causes of Death (WHO 1948). The rates are shown in Table 5

Bronchitis (B 32) and Pneumonia (B 31). The validity of comparing death-rates from bronchitis in the two countries seems very restricted. There is an extraordinary difference in clinical tradition regarding this disease entity as an underlying cause of death. This is stressed by Ustvedt (1958) who states, 'In Norway a patient, according to medical tradition, does not die *from* chronic bronchitis, but from the cardio-respiratory conditions characterizing the terminal stages of this disease In England & Wales this diagnosis seems generally accepted as an underlying cause of death, but even so transfers of deaths between the two diag-

TABLE 4

MORTALITY Age-standardized 40-46 years 1955

Male/female ratios

	Pneumonia and bronchitis	Tuberculosis of respiratory system	Total cardio-vascular	Arteriosclerotic and degenerative heart disease	Other diseases of heart	Malignant neoplasm of respiratory system	All other cancers	Senility ill-defined and unknown cases	Cardiorep.	All other diseases	All diseases
Austria	2.0	4.0	1.6	2.6	1.5	9.6	0.9	2.6	3.0	1.1	1.5
Belgium	5.1	5.8	1.8	2.8	1.6	8.7	0.8	2.0	3.0	1.2	1.6
Canada	2.1	2.3	2.0	3.1	1.5	5.0	0.8	2.0	3.0	1.0	1.5
Denmark	1.2	1.5	1.8	3.0	2.1	5.7	0.6	2.8	2.9	0.8	1.2
Finland	2.3	4.4	2.0	3.6	1.8	8.8	1.2	1.7	3.6	1.1	1.9
France	2.4	4.4	1.7	3.2	1.7	7.2	1.0	1.9	2.4	1.4	1.7
Italy	2.2	4.3	1.3	1.8	1.1	6.1	1.0				
Netherlands	2.8	2.5	1.6	2.7	1.4	12.7	0.7	3.4	3.2	0.9	1.3
New Zealand	2.8	2.2	1.7	3.2	1.7	8.8	0.7	3.0	3.3	0.9	1.4
Norway	1.1	2.7	1.7	3.3	1.5	3.0	0.9	2.6	2.7	1.0	1.4
Sweden	1.3	2.4	1.5	2.6	1.2	3.4	0.7	1.5	2.3	0.9	1.2
Switzerland	2.2	2.2	1.5	2.1	1.9	9.9	0.9	0.8	2.5	1.1	1.4
England & Wales	3.4	3.9	1.8	3.2	1.5	7.6	0.8	2.7	3.7	1.0	1.7
U.S.A. (White)	2.2	3.9	2.3	3.4	2.4	7.1	0.8	2.8	3.5	1.1	1.8

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The differences between countries in death-rates from B 31+32 are usually in the same direction in the two sexes. The rank correlation coefficient between male and female rates in the 14 countries is statistically significant ($r = 0.462$, $P = 0.0244$). The male/female ratios are closely correlated to the male death rates ($r = 0.6956$, $P = 0.0009$), but not significantly correlated to the female death-rates ($r = 0.1284$, $P = 0.5412$). In other words, the inter-country differences in mortality are *considerably more pronounced in the males than in the females*. The significance of this feature will be discussed in the section on environmental factors.

Mortality in England & Wales and Norway

The comparisons made above give strong support to the hypothesis that substantial *real* international differences exist in mortality from cardio-respiratory diseases in general, and probably also from bronchitis and pneumonia. It might be useful, however, to study in some more detail the mortality statistics of the two countries, i. e. England & Wales and Norway, showing the extreme values in death-rates from these diseases.

Age- and sex-specific rates have been calculated for 5-year groups between 40 and 64 years of age. The rates were calculated as averages for the period 1951-5 to reduce a possible effect of influenza epidemics on one-year respiratory rates, and also because of small numbers of deaths per year in some of the groups. Both countries have in the period under study followed the rules for certification and classification of causes of death laid down in the International Statistical Classification of Diseases, Injuries, and Causes of Death (WHO 1948). The rates are shown in Table 5.

Bronchitis (B 32) and Pneumonia (B 31). The validity of comparing death-rates from bronchitis in the two countries seems very restricted. There is an extraordinary difference in clinical tradition regarding this disease entity as an underlying cause of death. This is stressed by Ustvedt (1958) who states, 'In Norway a patient, according to medical tradition, does not die from chronic bronchitis, but from the cardio-respiratory conditions characterizing the terminal stages of this disease.' In England & Wales this diagnosis seems generally accepted as an underlying cause of death, but even so transfers of deaths between the two diag-

TABLE 5

MORTALITY England & Wales and Norway 1951 5

MALES — Rates per 100,000 per year

Age	Pneumonia and bronchitis		Tuberculous of respiratory system		Asthma, Bronchiectasis, Other diseases of lung		Total cardiovascular		Arteriosclerotic and degenerative heart disease	
	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	22.0	4.8	26.1	19.0	7.3	3.3	90.1	56.1	49.7	41.1
45-	49 4	5.5	36.0	27.0	12.8	5.5	187 4	116.6	114 1	67.7
50-	109 1	13 4	53.7	36.0	24 9	16.6	376.0	208.6	239.7	132.5
55-	212.9	20.2	66.0	35.0	41 4	17.5	674.5	411.5	421 1	241.8
60-	376.6	37.0	82.4	44.0	59 4	28.0	1197 4	708.6	738.0	384.4

MALES contd

Age	Other diseases of heart		Malignant neoplasm of respiratory system		All other cancers		Senility ill-defined and unknown causes		All diseases	
	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	4.0	4 9	25.2	4.7	48.5	45.5	0.1	11.7	277.9	198.0
45-	7.0	6.1	59 1	12.2	85.7	92.5	0.4	22.6	518.5	346.3
50-	12.7	17.5	124.3	24.7	153 6	132.2	0.4	35 1	979 4	590.8
55-	25.6	34.2	198.9	35 8	253.8	238.5	0.4	50.2	1664.0	1035.5
60-	45 1	67 9	250.2	46.5	412.1	388.2	0.6	67 1	2744 6	1516.5

FEMALES

Age	Pneumonia and bronchitis		Tuberculous of respiratory system		Asthma, Bronchiectasis, Other diseases of lung		Total cardiovascular		Arteriosclerotic and degenerative heart disease	
	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	11 1	3.6	14.8	14.0	6.2	4.3	56.5	25 9	9 9	5.0
45-	18.9	4.8	12.4	12.0	9.0	4.6	102.8	59.0	24 8	14.6
50-	30.2	7.2	12.6	12.0	11.6	8.7	190.9	124 1	55.7	28.2
55-	55.2	11 9	12.3	15 0	15.3	12.5	340.4	227.7	124.0	70.6
60-	104 9	29 4	14 1	14.0	21.5	14.7	649.5	479.3	280 1	160.0

FEMALES contd.

Age	Other diseases of heart		Malignant neoplasm of respiratory system		All other cancers		Senility Ill-defined and unknown causes		All d seases	
	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	3.3	2.3	5.8	0.8	85.6	80.0	0.1	4.8	235 0	177 9
45-	5.2	4.2	9.7	3.3	138.3	123.5	0.1	6.8	367.7	272.9
50-	9.5	9.8	14.8	5.7	205.5	190.5	0.2	7.7	572.9	429.3
55-	17 1	24.8	22.2	13 9	290.1	270.9	0.2	17.3	885.8	681 4
60-	29 1	46.0	31.7	14.7	387.5	372.0	0.3	30.0	1448.4	109

From: Central Bureau of Statistics of Norway Medical Statistical Report 1951–5
Registrar General's Statistical Review of England & Wales 1951–5.

Mortality E & W and Norway 1951 5
Males 40-64 years
Pneumonia and bronchitis

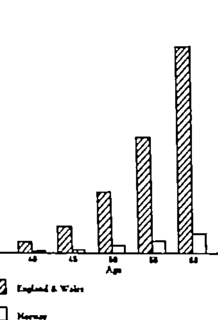


Fig. 1

Mortality E & W and Norway 1951 5
Males 40-64 years
Tuberculosis of respiratory system

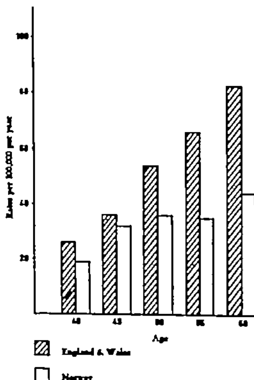


Fig. 2

Mortality E & W and Norway 1951 5
Males 40-64 years
Asthma, Bronchiectasis, Other diseases of lung

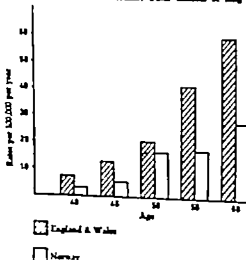


Fig. 3

TABLE 5

MORTALITY England & Wales and Norway 1951-5

MALES

Rates per 100,000 per year

Age	Pneumonia and bronchitis		Tuberculosis of respiratory system		Asthma, Bronchiectasis, Other diseases of lung		Total cardiovascular		Arteriosclerotic and degenerative heart disease	
	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	22.0	4.8	26.1	19.0	7.3	3.3	90.1	56.1	49.7	41.1
45-	49.4	5.5	36.0	27.0	12.8	5.5	187.4	116.6	114.1	67.7
50-	109.1	13.4	53.7	36.0	24.9	16.6	376.0	208.6	239.7	132.5
55-	212.9	20.2	66.0	35.0	41.4	17.5	674.5	411.5	421.1	241.8
60-	376.6	37.0	82.4	44.0	59.4	28.0	1197.4	708.6	738.0	384.4

MALES contd

Age	Other diseases of heart		Malignant neoplasm of respiratory system		All other cancers		Senility ill-defined and unknown causes		All diseases	
	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	4.0	4.9	25.2	4.7	48.5	45.5	0.1	11.7	277.9	198.0
45-	7.0	6.1	59.1	12.2	85.7	92.5	0.4	22.6	518.5	346.3
50-	12.7	17.5	124.3	24.7	153.6	132.2	0.4	35.1	979.4	590.8
55-	25.6	34.2	198.9	35.8	253.8	238.5	0.4	50.2	1664.0	1038.5
60-	45.1	67.9	250.2	46.5	412.1	388.2	0.6	67.1	2744.6	1516.5

FEMALES

Age	Pneumonia and bronchitus		Tuberculosis of respiratory system		Asthma, Bronchiectasis Other diseases of lung		Total cardiovascular		Arteriosclerotic and degenerative heart disease	
	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	11.1	3.6	14.8	14.0	6.2	4.3	56.5	25.9	9.9	5.0
45-	18.9	4.8	12.4	12.0	9.0	4.6	102.8	59.0	24.8	14.6
50-	30.2	7.2	12.6	12.0	11.6	8.7	190.9	124.1	55.7	28.2
55-	55.2	11.9	12.3	15.0	15.3	12.5	340.4	227.7	124.0	70.6
60-	104.9	29.4	14.1	14.0	21.5	14.7	649.5	479.3	280.1	160.0

FEMALES contd.

Age	Other diseases of heart		Malignant neoplasm of respiratory system		All other cancers		Senility ill-defined and unknown causes		All diseases	
	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	3.3	2.3	5.8	0.8	85.6	80.0	0.1	4.8	235.0	177.9
45-	5.2	4.2	9.7	3.3	138.3	123.5	0.1	6.8	367.7	272.9
50-	9.5	9.8	14.8	5.7	205.5	190.5	0.2	7.7	572.9	429.3
55-	17.1	24.8	22.2	13.9	290.1	270.9	0.2	17.3	885.8	681.4
60-	29.1	46.0	31.7	14.7	387.5	372.0	0.3	30.0	1448.4	1095.6

From: Central Bureau of Statistics of Norway Medical Statistical Report 1951-5.
Registrar General's Statistical Review of England & Wales 1951-5

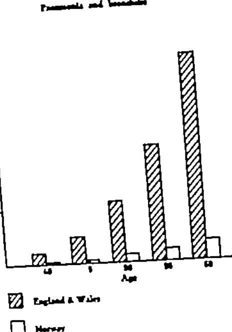

Mortality E & W and Norway 1951 5
Males 40-64 years
Age
England & Wales
Norway

Fig. 1

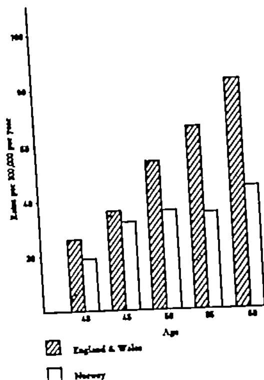
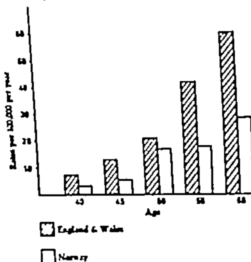

Mortality E & W and Norway 1951 5
Males 40-64 years
Age
England & Wales
Norway

Fig. 2


Mortality E & W and Norw y 1951 5
Males 40-64 years
Age
England & Wales
Norw y

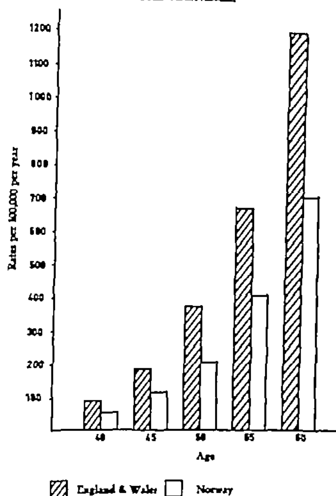


Fig. 4

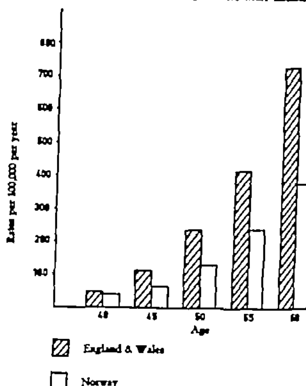
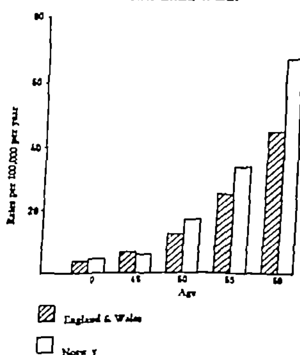


Fig. 5



nostic groups are to be suspected. The General Register Office has in its reports commented on this on numerous occasions, also in recent years. 'The proportion of respiratory mortality in elderly persons attributed to bronchitis continues to decrease and that attributed to pneumonia to increase (1956). 'Though clinically pathologically and epidemiologically distinct, these four conditions (influenza, bronchitis, pneumonia, bronchiec

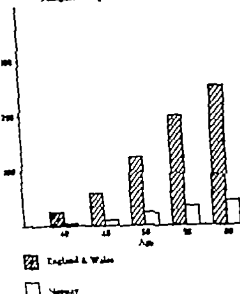


Fig. 7

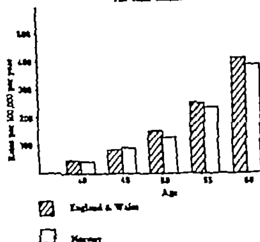


Fig. 8

tasis) ha e much in common as causes of death. They are often reported in association upon death-certificates, and the assignment of death to one condition rather than another may depend much upon the nosological preference of the certifying practitioners (1958).

In the table, Bronchitis (B 32) is therefore pooled with Pneumonia (B 31). This combined group shows a marked difference in rates between the two countries. In both sexes and in all age-groups the rates are higher in England & Wales than in Norway From Table 6, giving the ratios between the rates in England & Wales and Norway it will be seen that this

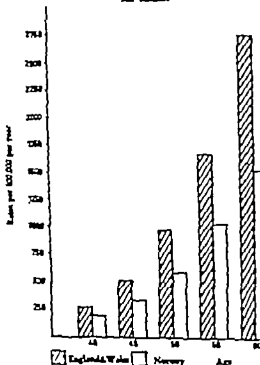


Fig. 9

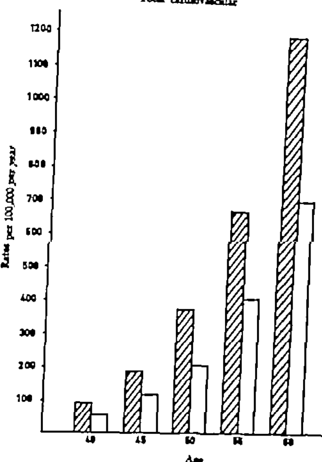


Fig. 4

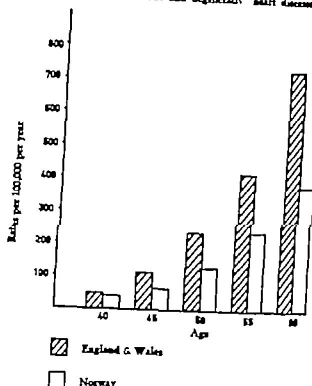


Fig. 5

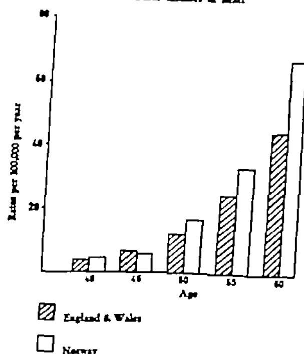


Fig. 6

nostic groups are to be suspected. The General Register Office has in its reports commented on this on numerous occasions, also in recent years. "The proportion of respiratory mortality in elderly persons attributed to bronchitis continues to decrease and that attributed to pneumonia to increase (1956). "Though clinically pathologically and epidemiologically distinct, these four conditions (influenza, bronchitis, pneumonia, bronchiec

TABLE 7

MORTALITY 1951 5 England & Wales and Norway

Male/female ratios

	Pneumonia and bronchitis		Tuberculosis of respiratory system		Asthma Bronchiectasis, Other diseases of lung		Total cardiovascular		Arteriosclerotic and degenerative heart disease	
Age	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	2.0	1.3	1.8	1.3	1.2	0.8	1.6	2.2	5.0	8.2
45-	2.6	1.2	2.9	2.3	1.4	1.2	1.8	2.0	4.4	4.6
50-	3.4	1.9	4.3	3.0	2.1	1.9	2.0	1.7	4.3	4.7
55-	3.9	1.7	5.4	2.3	2.7	1.4	2.0	1.8	3.4	3.4
60-	3.6	1.3	5.8	3.1	2.8	1.9	1.9	1.5	2.6	2.4

	Other diseases of heart		Malignant neoplasms of respiratory system		All other cancers		Senility ill-defined and unknown causes		All diseases	
Age	E&W	N	E&W	N	E&W	N	E&W	N	E&W	N
40-	1.2	2.1	4.3	5.9	0.6	0.6	1.0	2.4	1.2	1.1
45-	1.3	1.5	6.1	3.7	0.6	0.7	4.0	3.3	1.4	1.3
50-	1.3	1.8	8.4	4.3	0.7	0.7	2.0	4.6	1.7	1.4
55-	1.5	1.4	9.0	2.6	0.9	0.9	2.0	2.9	1.9	1.3
60-	1.5	1.5	7.9	3.2	1.1	1.0	2.0	2.2	1.9	1.4

Malignant neoplasms of the respiratory system (160-5). This group of diseases shows a still larger difference in rates between the two countries, both in males and in females. There is little difference in the rates from All other cancers' thus reducing the possibility of major diagnostic differences accounting for the excess in England & Wales of malignant disease with this localisation.

Other and unspecified heart diseases (B 27). In this group we find the inverse tendency in mortality in that the Norwegian rates are highest in nearly all age-groups in both sexes, and the difference between the countries increases with ad ancing age. As this diagnostic group includes a variety of conditions, it is difficult to interpret these figures. Splitting it up into subgroups gives little additional information, as the numbers then become very small and the observed differences in each subgroup may be due entirely to chance variation. It seems justified however on clinical grounds, to suggest that in this group which includes cor pulmonale one may find cases in Norway that in England & Wales would be classified as chronic bronchitis However even if all deaths in this

ratio increases with age from 4 6 in the 40-44 to 10 6 in the 55-59 year age-group for males, and seems to *decrease in the* higher age-groups. Both the differences in the rates and the *increase of the* ratio with age are less, although present also in the females.

TABLE 6

MORTALITY 1951 5

Ratios England & Wales/Norway

Age	Pneumonia and bronchitis		Tuberculosis of respiratory system		Asthma Bronchiectasis. Other diseases of lung		Total cardiovascular		Arteriosclerotic and degenerative heart disease	
	M	F	M	F	M	F	M	F	M	F
40-	4.6	3.0	1 4	1 1	2.2	1 4	1 6	2.1	1.2	2.0
45-	8.9	4 0	1.3	1.0	2.3	1.9	1.6	1.7	1.7	1.7
50-	8.1	4.3	1.5	1 1	1.5	1.3	1.8	1.5	1.8	2.0
55-	10.6	4.6	1.9	0.8	2.4	1.2	1.7	1.3	1.7	1.8
60-	10.2	3.6	1.9	1.0	2.1	1.5	1.7	1 4	1 9	1.8

Age	Other diseases of heart		Malignant neoplasm of respiratory system		All other cancers		Senility ill-defined and unknown causes		All diseases	
	M	F	M	F	M	F	M	F	M	F
40-	0.8	1 4	5 4	7.3	1 1	1 1	0.01	0.02	1 4	1.3
45-	1 1	1.2	4.8	2.9	0.9	1 1	0.02	0.01	1.5	1.3
50-	0.7	1.0	5.0	2.6	1.2	1.1	0.01	0.03	1.7	1.3
55-	0.7	0.7	3.6	1.6	1 1	1 1	0.01	0.01	1.6	1.3
60-	0.7	0.6	5 4	2.2	1.1	1.0	0.01	0.01	1.8	1.3

Respiratory tuberculosis (B 1) In the males the rates in all age-groups are higher in England & Wales than in Norway showing a slightly increasing difference with age. The female rates are very similar in the two countries, and in all age-groups lower than the corresponding male rates. In both countries the male/female ratio increases with age.

Asthma bronchiale Bronchiectasis Emphysema (241 525 7) There is a marked excess mortality in England & Wales from these causes also, more pronounced for the bronchiectasis-emphysema group than for bronchial asthma. The difference between the countries is most marked in males, and increases with age.

TABLE 8

MORTALITY England & Wales and Norway 1951-5

Death rates per 100,000 per year

	MALES				*FEMALES*			
	Cardio-resp. diseases		All other diseases		Cardio-resp. diseases		All other diseases	
Age	E&W	N	E&W	N	E&W	N	E&W	N
40-	170.8	99.6	107.1	98.4	94.5	53.4	140.5	124.5
45-	345.1	189.4	173.4	156.9	152.9	90.5	214.8	182.4
50-	648.4	334.4	291.0	254.4	260.3	165.4	312.6	263.9
55-	1194.1	570.2	469.9	465.3	445.6	298.3	440.2	383.1
60-	1966.6	931.2	778.0	585.3	822.0	582.1	626.4	513.5

Ratios England & Wales/Norway

	Cardio-resp. diseases		All other diseases	
Age	M	F	M	F
40-	1.7	1.8	1.1	1.1
45-	1.8	1.7	1.1	1.2
50-	2.1	1.6	1.1	1.2
55-	2.1	1.5	1.0	1.2
60-	2.1	1.4	1.3	1.2

Male/female ratios England & Wales and Norway

	Cardio-resp. diseases		All other diseases	
Age	E&W	N	E&W	N
40-	1.8	1.9	0.8	0.8
45-	2.3	2.1	0.8	0.8
50-	2.6	2.0	0.9	1.0
55-	2.7	1.9	1.1	1.2
60-	2.4	1.6	1.2	1.1

Summing up the result of this comparison of mortality by cause in England & Wales and Norway it seems justified to draw the conclusion that the large differences observed in recorded mortality from chronic respiratory diseases reflect *real* differences, and cannot be explained as statistical *artifacts* caused by different habits of diagnosis or certification of causes of death.

Time trend in mortality from chronic respiratory diseases

One of the most striking features emerging from the study of mortality statistics on chronic respiratory disease, is the present excess male mortality in middle-aged persons. Regarding cancer of the lung, it has been shown that this sex difference is caused by the occurrence of a new epidemiological situation — a tremendous rise in male mortality within *the last few decades*. It would therefore be of interest to see whether the same change in the sex ratio has also taken

category are transferred to B 31+32, the observed differences in the rates remain very large.

Total cardiovascular disease (B 22 B 24-29 85-86) In both sexes we find an excess mortality in England & Wales compared with Norway The maximum difference is found in the 40-44-year age-group in females and in the 50-55-year age-group in males.

Senility without mention of psychosis ill-defined and unknown causes (B 45). In this group there is a very marked difference between the countries. The Norwegian rates are of the same order as the rates for 'Bronchitis and pneumonia whereas the rates in England & Wales are negligible. This disparity may be due to differences in administrative procedure for registration and recording of causes of death, or to differences regarding the stringency in diagnosis required to allocate a death to a specific classification group In rural districts of Norway a number of deaths still occur without medical attention, and in such cases the cause of death stated by relatives is registered in the mortality statistics (Backer 1949) This might tend to inflate the rates of ill-defined conditions. From the detailed tables in the Medical Statistical Report (1951 1952, 1953 1954 1955) from the Central Bureau of Statistics of Norway (1954 1955 1956 1957 1958) it is seen that most of the cases in this group in the age-groups under study refer to Acute heart failure' (782.4) and Sudden death (cause unknown) (795.2). It is not likely that the majority of these deaths in England & Wales would be diagnosed or classified as bronchitis and pneumonia. However even if one transfers all deaths classified in Norway under B 45 to B 31+32, the rates in the latter group are still markedly lower than the corresponding rates for England & Wales in both sexes in all age-groups. In Table 8 all the cardiovascular respiratory diseases have been grouped together with B 45 It emerges that the difference observed between the countries in total disease mortality is mainly due to an excess mortality from cardiovascular respiratory diseases, and also that the adverse male experience in both countries is limited to these diseases.

Data on multiple causes of death by sex and age are not published in any detail in either of the two countries. The Central Bureau of Statistics of Norway (Mr B Bendiksen) has most kindly made available cross-tabulations of multiple causes for cases where respiratory diseases were mentioned on the death certificate. The numbers are rather small in each group, but consistent from one year to another From these figures it seems reasonable to assume that no significant under recording of these diseases as an underlying cause of death takes place in Norway Even if all deaths where bronchitis is mentioned on the death certificate either as a complication or as a contributory cause were recorded as bronchitis in the single-cause classification, the general picture in comparisons between England & Wales and Norway would not be altered.

TABLE 10

MORTALITY

Geographical differences in bronchitis mortality in England & Wales

1911-20

Age	25–		35–		45–		55–		65–		75+	
	M	F	M	F	M	F	M	F	M	F	M	F
E & W	100	100	100	100	100	100	100	100	100	100	100	100
London	133	84	157	118	148	127	125	119	125	116	136	126
C. B.	142	134	149	143	146	131	146	147	139	136	124	119
U. D.	76	90	69	82	77	76	87	85	93	91	95	92
R. D.	51	66	39	47	39	44	46	48	58	61	77	79

Registrar General Decennial Supplement, England & Wales 1921 Part III, HMSO 1933

1920-30

Age	25–		35–		45–		55–		65–		75+	
	M	F	M	F	M	F	M	F	M	F	M	F
E & W	100	100	100	100	100	100	100	100	100	100	100	100
London	133	87	137	105	152	111	132	115	112	106	109	109
C. B.	127	132	140	140	140	143	134	140	130	131	112	119
U. D.	86	90	83	86	80	83	90	87	98	93	97	95
R. D.	59	71	43	50	39	50	50	50	63	63	85	81

Registrar General's Decennial Supplement, England & Wales 1931 Part III, HMSO 1952

1950-3

Age	15–		45–		65+	
	M	F	M	F	M	F
E & W	100	100	100	100	100	100
Gr London	97	94	112	99	130	122
Conurbations	124	117	130	127	133	127
Urban 100,000	115	117	109	102	107	102
Urban 50-100,000	94	106	93	92	89	84
Urban 50,000	91	94	86	86	84	83
Rural	52	72	52	59	65	74

Registrar General' Decennial Supplement, England & Wales 1951 Area Mortality HMSO 1958

place in other chronic respiratory diseases. As pointed out previously the exami nation of time trends in mortality from different causes is severely handicapped by the numerous changes in medical and vital statistical practice which have taken place in this century One possible method of reducing the errors that may thus be introduced, is to study the time trend of the male/female ratio. This ratio will be less affected by the different changes, as there is little reason to believe that any change in diagnosis and certification has influenced the recorded mortality differently in the two sexes. This method will unfortunately not eliminate bias that might be introduced by a tendency to over record causes known to be preponderant in one sex, for example male preponderance in cancer of the lung. Fonseka (1958) suggested that this factor influenced the certification habits in the U.K. in cardiovascular diseases. There is, however no suggestion to the effect that this factor may account for major differences in the male/female ratio

Table 9 gives the male/female ratios from bronchitis in England & Wales for the decades 1911 20 1921 30 and 1950-3 We find that in 1911 20 there was

TABLE 9

MORTALITY

Male/female ratios. Bronchitis. England & Wales

	1911 20				1921 30			
	45–	55–	65–	75+	45–	55–	65–	75+
E & W	1.30	1.20	1 14	1.09	1.83	1.26	1.20	1.12
London	1.52	1.26	1.22	1 18	2.50	1 45	1.27	1 11
C. B.	1.26	1 19	1 17	1 13	1.80	1.21	1 17	1 12
U D	1.32	1.23	1.17	1.12	1.75	1.29	1.26	1 15
R. D	1 15	1.16	1.08	1.07	1.45	1.28	1.20	1 18

1950-3

	45–	65+
E & W	4.38	2.00
Gr London	5.00	2.14
Conurbations	4 47	2.09
Urban 100,000	4.66	2.09
Urban 50-100,000	4 47	2.10
Urban 50,000	4.38	2.03
Rural	3.86	1.75

Calculated from Registrar General's Decennial Supplement, England & Wales 1951 Area Mortality HMSO 1958

TABLE 10

MORTALITY

Geographical differences in bronchitis mortality in England & Wales

1911-20

Age	25–		35–		45–		55–		65–		75+	
	M	F	M	F	M	F	M	F	M	F	M	F
E & W	100	100	100	100	100	100	100	100	100	100	100	100
London	135	84	137	118	148	127	125	119	125	116	136	126
C. B.	142	134	149	143	144	151	146	147	139	136	124	119
U. D.	76	90	69	82	77	74	87	83	90	91	95	92
R. D.	51	66	59	67	55	44	46	48	58	61	77	79

Registrar General's Decennial Supplement, England & Wales 1921, Part III, HMSO 1933

1921-30

Age	25–		35–		45–		55–		65–		75+	
	M	F	M	F	M	F	M	F	M	F	M	F
E & W	100	100	100	100	100	100	100	100	100	100	100	100
London	133	87	137	105	152	111	132	115	112	106	109	109
C. B.	127	132	140	140	142	143	134	140	130	131	112	119
U. D.	86	90	83	86	83	83	95	87	98	93	97	95
R. D.	59	71	43	50	39	50	50	50	63	63	85	81

Registrar General's Decennial Supplement, England & Wales 1931, Part III HMSO 1937

1950-3

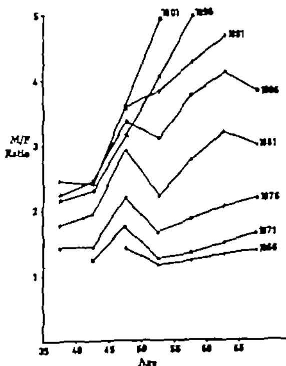
Age	15–		45–		65+	
	M	F	M	F	M	F
E & W	100	100	100	100	100	100
Gr London	97	94	112	99	130	122
Conurbations	124	117	130	127	133	127
Urban 100,000	115	117	129	102	107	102
Urban 50-100,000	94	108	93	92	89	84
Urban 50,000	91	94	86	86	84	83
Rural	52	72	52	59	65	74

Registrar General's Decennial Supplement, England & Wales 1951 Area Mortality HMSO 1958

a slight excess mortality in males, whereas by 1950-3 the ratio had increased to more than 4 in the 45-64-year age-group. The increase in higher age-groups is less pronounced. This strongly suggests that the unfavourable death-experience in the males compared with females is something relatively new in the epidemiology of bronchitis. It is of interest that this adverse male experience seems to be rather uniform in different geographical areas. From Table 10 it will be seen that the gradient in mortality from rural districts to larger cities and conurbations in both sexes is practically the same as 40 years ago.

Figures 10-12 show the time trend of the male/female ratio for bronchitis, respiratory tuberculosis and cancer of the lung in England & Wales. The curves are strikingly similar. For all these diseases middle-aged males have from c. 1920 onwards experienced an increasingly unfavourable mortality compared with the females, and the changes in the ratios in all the diseases seem to start in the same cohort, i. e. persons born in 1881-5. These similarities in trends reduce the possibility of diagnostic transfers accounting for the changes in the ratio of any particular disease, and may suggest common factors influencing the mortality pattern of most respiratory diseases. This does not, however, imply that the

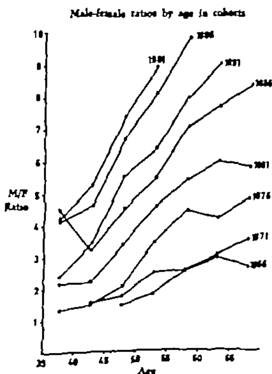
Mortality from pneumonia and bronchitis E&W
Male-female ratios by age in cohorts



Data from: Case, R. A. M., Harley, J. L. (1958)

Fig. 10

Mortality from malignant neoplasm of lung and pleura E&W

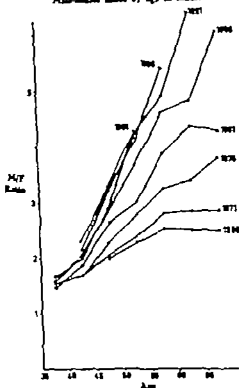


Data from Registrar General's Stat. Rev. E&W 1955 Commentary

Fig. 11

mortality rates in the different diseases show similar trends. These rates, which admittedly are subject to many inaccuracies, suggest that the increase in the male/female ratio for respiratory cancer is caused by a much steeper increase in male than in female mortality rates, whereas for respiratory tuberculosis and bronchitis the increasing ratios are mainly due to a substantial decrease in the female death-rates and a smaller decrease in the male rates. This suggests that males profit less from the various measures introduced in the last decades for the treatment of respiratory tuberculosis and bronchitis.

For most countries mortality statistics for previous decades are not available in a form which permits examination of the time trends for different causes of death. In Norway it is impossible to follow the secular trend in mortality from bronchitis and pneumonia by age and sex (Central Bureau of Statistics of Norway 1959) This is due to the numerous changes in classification rules in this century (Backer 1949), and to the small number of deaths from these causes making the calculation of comparability factors futile. For respiratory tuberculosis one may possibly assume that changes in classification rules have had a minor effect. Figure 14 shows the time trend of the male/female ratio for this diagnostic group in Norway and Figure 13 shows the trend for respiratory cancers. There are marked differences from the trends observed in England & Wales. Excess male mortality from tuberculosis is found in both countries, but it is considerably more pronounced in England & Wales, and the change in the male/female ratio takes place about 70 years later in Norway. In respiratory cancer the present male/female ratios are of the same order of magnitude between 40 and 59 years of age in the two countries, but similarly in this disease entity the male excess does not appear in Norway until the 1940-9 decade. Kreyberg (1954), assuming a period of about 20 years for respiratory cancer to develop, draws the conclusion from a study of lung cancer in Norway that



Data from Case R A M., Harley J L. (1955)

Fig. 12

from c 1920 new etiological factors began to operate, and these factors affected the males much more than the females.

Morbidity in England & Wales and Norway

The finding of substantial real differences in mortality in different countries raises the question of whether this is due to similar differences in morbidity in the populations. As mentioned in the general discussion of morbidity statistics, data on morbidity in the total population are not available in most countries, but in England & Wales and Norway comprehensive statistics are published on morbidity by cause in the total working population.

A certain degree of comparability is conceivable from the almost identical rules for claims of sickness benefit in the two sickness insurance schemes, and in order to test the comparability rates have been calculated for a number of conditions apart from the diseases under study. The statistics in England & Wales are published on a national scale, referring to the working population in the whole country. In Norway data are unfortunately published for each administrative area separately, referring to the persons employed within the area. The following comparisons are therefore made between the working populations in England & Wales and in the Norwegian towns of Oslo and Bergen

Mortality from malignant neoplasm of lung and pleura, Norway

Male-female ratios by age in cohorts

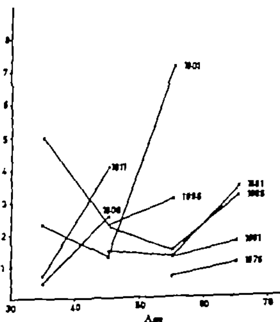


Fig. 13

Total mortality from tuberculosis, Norway

Male-female ratios by age in cohorts

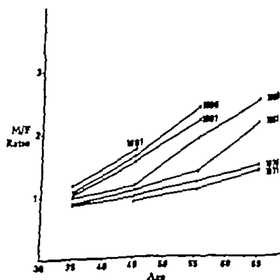


Fig. 14

(the two largest urban areas in Norway with a population of 444 000 and 113,000 respectively in 1954). The Norwegian rates are thus evidently not representative for the country as a whole, but assuming a similar rural-urban gradient in respiratory morbidity as has been found in England & Wales (Table 10) this bias would tend to lessen any *differences found in the comparisons.* Even if nothing is known of a possible urban-rural gradient in Norway apart from that found in cancer of the lung, there is no reason to believe that respiratory diseases in general are more frequent in other parts of Norway than in the larger towns. The data from England & Wales are classified according to the International Statistical Classification of Diseases, Injuries, and Causes of Death (WHO 1948); the Norwegian data are classified according to a *special classification in use by Norwegian* trygdekasser' (health insurance). As both statistics are based on a single cause certified by a physician in a specific medical diagnostic term, for example 'bronchitis' one may assume that this *difference in classification* will *not* be of *decisive* importance for the rates compared.

Table 11 gives the figures for claims on sickness insurance schemes for spells of *illness* lasting more than 3 days, *in England & Wales, Oslo and Bergen.* The rates are calculated as averages over a 3-year period to reduce the influence of epidemics on single year rates. Comparing the two Norwegian towns one finds that in both sexes in all age-groups the rates for bronchitis and pneumonia are higher in Oslo than in Bergen. The rates for influenza are consistently higher in Bergen than in Oslo. This may suggest that some transfers between these diagnostic groups may take place in Norway. In the other diseases for which rates are calculated, there is a tendency towards slightly higher rates in Oslo in both sexes. The differences are small, however and in view of the uncertainties involved in this type of data no inferences can be made.

For the convenience of comparisons, ratios between the rates in England & Wales and Oslo were calculated. The results are given in Table 12. In bronchitis and pneumonia there is an excess morbidity in England & Wales in both sexes in all age-groups. The ratio increases with age, most markedly in the males. Influenza and asthma also have higher morbidity in England & Wales, with no age-gradient in the ratio for influenza and a decreasing ratio with age in asthma. In the other diagnostic groups as well as for total *morbidity* there are only minor differences between males in the two countries, *suggesting* that there are probably no major differences in the composition of the basic populations. The females show a less consistent feature. This may be an *effect of differences* in the composition of the female working population in the two countries, as one can assume that selective factors are much more important in females than in males in any working population.

Table 13 gi es the duration of spells of illness in England & Wales and Oslo. For all the different respiratory conditions the average duration is longer in

TABLE 11

MORBIDITY in working population England & Wales Oslo and Bergen

Spells of illness per 1,000 insured persons per year (3 years average)

MALES

	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
Age	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	5.3	5.4	7.5	4.3	4.6	3.5	1.8	1.9	1.6	2.6	0.7	1.4	51.2	16.4	25.7	16.8	13.9	10.5	284.9	238.1	204.7
30-	7.8	9.0	9.1	2.6	2.9	2.4	2.3	2.3	1.6	2.2	0.9	1.0	51.0	18.9	27.5	22.7	17.5	14.0	290.0	257.9	228.2
40-	9.6	10.0	9.1	1.9	2.1	1.2	3.5	3.1	3.3	2.9	1.7	1.6	45.8	18.1	29.9	34.0	21.6	15.6	289.6	290.7	237.2
50-	11.1	8.7	7.2	1.5	1.3	0.8	5.1	5.5	4.1	4.1	2.9	1.4	46.5	17.4	26.8	65.8	27.9	21.6	353.8	313.0	240.9
60-	9.1	7.2	3.7	1.0	1.2	0.9	5.1	7.2	8.2	4.8	3.5	1.2	41.7	18.4	22.2	96.5	34.3	21.7	396.6	336.2	223.1

FEMALES

	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
Age	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	1.1	2.4	2.4	7.1	8.8	4.7	0.3	0.6	0.3	2.4	1.0	1.1	49.8	19.9	33.2	20.5	16.2	12.0	369.6	386.2	289.7
30-	2.1	4.2	3.6	3.8	3.8	3.7	0.5	1.1	0.6	2.8	1.2	1.4	43.3	22.5	37.3	29.3	23.7	14.5	343.5	430.0	331.5
40-	2.7	5.3	3.7	1.7	1.8	1.3	0.9	1.5	1.3	3.3	1.8	1.5	40.5	21.7	35.4	34.4	23.8	17.1	331.0	392.3	307.0
50-	2.4	4.4	2.5	1.0	1.3	1.0	1.1	1.5	1.1	2.8	2.1	1.6	36.6	19.7	31.7	41.4	27.7	17.5	308.5	354.9	254.9
60-	1.4	2.3	2.3	0.5	1.1	0.5	0.8	1.7	1.5	1.5	2.3	1.7	28.7	10.0	13.9	40.4	21.6	13.1	234.4	255.9	163.0

Calculated from Digest of Statistics Analysing Certificates of Incapacity 1953/4 1954/5 1955/6, Min. of Pensions & National Insurance.
— " — Arsberetning for Oslo Trygdekasse 1953-5
— " — Arsberetning for Bergen Trygdekasse 1953-5

England & Wales than in Norway It is impossible, however to draw any conclusions from this as to the seriousness of the illness, because the duration of all other diseases in the table is also consistently longer in England & Wales. This rather suggests a general tendency to longer sickness absences from any disease in England & Wales compared with Norway This may be due to variation in morale, medical care or other socio-economic factors.

It has been pointed out earlier in this paper that morbidity rates in working

TABLE 12

Morbidity (Spells of illness)

Ratios England & Wales/Oslo 1953-5

	Peptic ulcer		Appendicitis		Hernia		Asthma		Influenza		Bronchitis & Pneum.		All diseases	
Age	M	F	M	F	M	F	M	F	M	F	M	F	M	F
20-	1.0	0.5	0.9	0.8	1.0	0.5	3.7	2.4	3.1	2.5	1.2	1.3	1.2	1.0
30-	0.9	0.5	0.9	1.0	1.0	0.4	2.4	2.3	2.6	1.9	1.3	1.2	1.1	0.8
40-	1.0	0.3	0.9	1.0	1.1	0.6	1.7	1.8	2.5	1.9	1.4	1.3	1.0	0.8
50-	1.3	0.6	1.2	0.8	0.9	0.7	1.4	1.3	2.7	1.9	2.4	1.5	1.1	0.9
60-	1.3	0.6	0.8	0.3	0.7	0.5	1.4	0.7	2.3	2.9	2.8	1.9	1.2	0.9

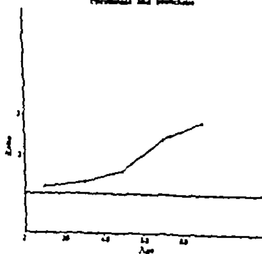


Fig. 15

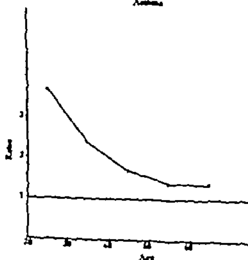


Fig. 16

TABLE 11

MORBIDITY in working population England & Wales Oslo and Bergen

Spells of illness per 1,000 insured persons per year (3 years average)

MALES

Age	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	5.3	5.4	7.5	4.3	4.6	3.5	1.8	1.9	1.6	2.6	0.7	1.4	51.2	16.4	25.7	16.8	13.9	10.5	284.9	238.1	204.7
30-	7.8	9.0	9.1	2.6	2.9	2.4	2.3	2.3	1.6	2.2	0.9	1.0	51.0	18.9	27.5	22.7	17.5	14.0	290.0	257.9	228.2
40-	9.6	10.0	9.1	1.9	2.1	1.2	3.5	3.1	3.3	2.9	1.7	1.6	45.8	18.1	29.9	34.0	21.6	15.6	289.6	290.7	237.2
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FEMALES

Age	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	1.1	2.4	2.4	7.1	8.8	4.7	0.3	0.6	0.3	2.4	1.0	1.1	49.8	19.9	33.2	20.5	16.2	12.0	369.6	386.2	289.7
30-	2.1	4.2	3.6	3.8	3.8	3.7	0.5	1.1	0.6	2.8	1.2	1.4	43.3	22.5	37.3	29.3	23.7	14.5	343.5	430.0	331.5
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60-	1.4	2.3	2.3	0.5	1.1	0.5	0.8	1.7	1.5	1.5	2.3	1.7	28.7	10.0	13.9	40.4	21.6	13.1	234.4	255.9	163.0

Calculated from Digest of Statistics Analyung Certificates of Incapacity 1953/4 1954/5 1955/6, Min. of Pensions & N tional Insurance.
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Morbidity (Spells of illness)

Ratios England & Wales/Oslo 1953-5

	Peptic ulcer		Appen-dicitis		Hernia		Asthma		Influenza		Bronchitis & Pneum.		All diseases	
Age	M	F	M	F	M	F	M	F	M	F	M	F	M	F
20-	1.0	0.5	0.9	0.8	1.0	0.5	3.7	2.4	3.1	2.5	1.2	1.3	1.2	1.0
30-	0.9	0.5	0.9	1.0	1.0	0.4	2.4	2.3	2.6	1.9	1.3	1.2	1.1	0.8
40-	1.0	0.5	0.9	1.0	1.1	0.6	1.7	1.8	2.5	1.9	1.6	1.5	1.0	0.8
50-	1.3	0.6	1.2	0.8	0.9	0.7	1.4	1.3	2.7	1.9	2.4	1.5	1.1	0.9
60-	1.3	0.6	0.8	0.5	0.7	0.5	1.4	0.7	2.3	2.9	2.8	1.9	1.2	0.9

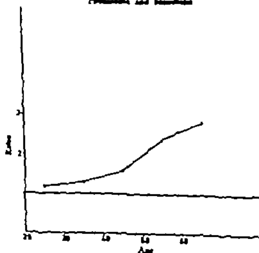


Fig. 15

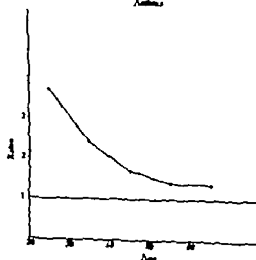


Fig. 16

TABLE 11

MORBIDITY in working population England & Wales Oslo and Bergen

Spells of illness per 1,000 insured persons per year (3 years average)

MALES

	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
Age	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	5.3	5.4	7.5	4.3	4.6	3.5	1.8	1.9	1.6	2.6	0.7	1.4	51.2	16.4	25.7	16.8	13.9	10.5	284.9	238.1	204.7
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60-	9.1	7.2	3.7	1.0	1.2	0.9	5.1	7.2	8.2	4.8	3.5	1.2	41.7	18.4	22.2	96.5	34.3	21.7	396.6	336.2	223.1

FEMALES

	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
Age	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	1.1	2.4	2.4	7.1	8.8	4.7	0.3	0.6	0.3	2.4	1.0	1.1	49.8	19.9	33.2	20.5	16.2	12.0	369.6	386.2	289.7
30-	2.1	4.2	3.6	3.8	3.8	3.7	0.5	1.1	0.6	2.8	1.2	1.4	43.3	22.5	37.3	29.3	23.7	14.5	343.5	430.0	331.5
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60-	1.4	2.3	2.3	0.5	1.1	0.5	0.8	1.7	1.5	1.5	2.3	1.7	28.7	10.0	13.9	40.4	21.6	13.1	234.4	255.9	163.0

Calculated from Digest of Statistics Analysing Certificates of Incapacity 1953/4 1954/5 1955/6 Min. of Pensions & National Insurance.
— — Årberetning for Oslo Trygdekasse 1953-5
— — Årberetning for Bergen Trygdekasse 1953-5

populations are influenced by occupational factors. It would therefore have been of interest to study comparable data for selected occupational groups in the two countries. To the author's knowledge, no reliable statistics of this type have been published concerning Norway

Summing up this examination of available morbidity data, it seems justifiable to suggest that in the working population at least, there is a higher morbidity from respiratory illness in England & Wales than in Norway as measured in spells of illness. The difference, however is not as large as the one found in mortality This may suggest that certain respiratory diseases run a more serious course with a higher case fatality rate in England & Wales.

Morbidity (spells of illness)
Ratios E+W/Oslo 1953-5. Male working population
All diseases

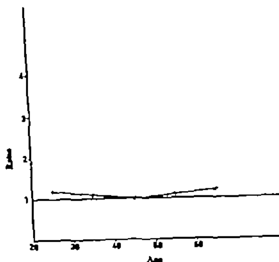


Fig. 21

Environmental factors

In most studies of the epidemology of chronic bronchitis and pneumonia, two factors have been found to be of decisive importance: atmospheric pollution and cigarette-smoking.

ATMOSPHERIC POLLUTION

The effect on mortality and morbidity of exposure to relatively high concentrations of atmospheric pollution is well known. According to Ashe (1959) the earliest written record of death from air pollution appears in the writing of Pliny the Younger (first century A.D), who tells that his uncle went by ship to see what was happening as a result of the eruption of Mount Vesuvius in A.D 79 The old gentleman was the victim of chronic bronchitis or some more extensive chronic pulmonary disease before the trip Nearing the site he was overcome by sulphurous fumes and died on the third day after his collapse.

Morbidity (spells of illness)
Ratios E+W/Oslo 1953-5 Male working population
Influenza

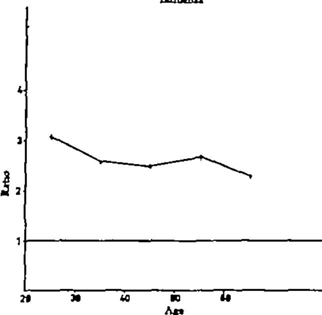


Fig. 17

Morbidity (spells of illness)
Ratios E+W/Oslo 1953-5. Male working population
Peptic ulcer

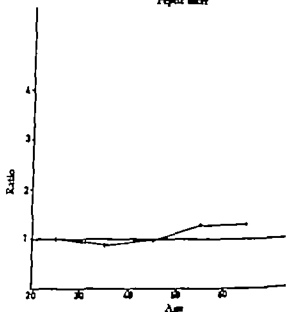


Fig. 18

Morbidity (spells of illness)
Ratios E+W/Oslo 1953-5 Male working population
Hernia

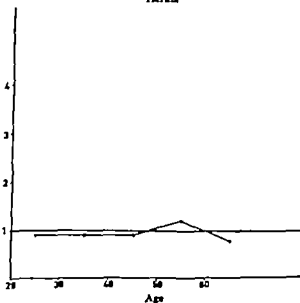


Fig. 19

Morbidity (spells of illness)
Ratios E+W/Oslo 1953-5 Male working population
Appendicitis

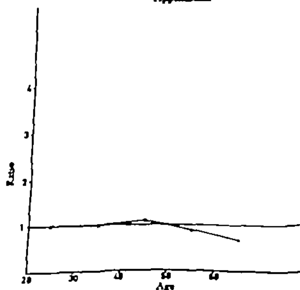


Fig. 20

populations are influenced by occupational factors. It would therefore have been erest to study compar ata for selected occupa- groups in the two ries. To the author s ledge, no reliable statis- f this type have been shed concerning Nor

mming up this examina of available morbidity , it seems justifiable to est that in the working ilation at least, there is gher morbidity from res- tory illness in England Vales than in Norway as sured in spells of illness. difference, however is as large as the one found in mortality This may suggest that certain respira y diseases run a more serious course with a higher case fatality rate in Eng d & Wales.

Morbidity (spells of illness)
Ratios E+W/Oslo 1953-5. Male working population
All diseases

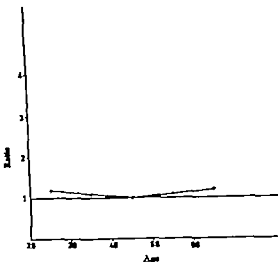


Fig. 21

Environmental factors

most studies of the epidemiology of chronic bronchitis and pneumonia, two ctors have been found to be of decisive importance: atmospheric pollution d cigarette-smoking.

TMOSPHERIC POLLUTION

he effect on mortality and morbidity of exposure to relatively high concen- ations of atmospheric pollution is well known. According to Ashe (1959) the rliest written record of death from air pollution appears in the writing of liny the Younger (first century A.D) who tells that his uncle went by ship) see what was happening as a result of the eruption of Mount Vesuvius in .D 79 The old gentleman was the victim of chronic bronchitis or some more xtensive chronic pulmonary disease before the trip. Nearing the site he was vercome by sulphurous fumes and died on the third day after his collapse.

TABLE 13

MORBIDITY in working population England & Wales Oslo and Bergen

Average duration (days) per spell of illness (3 years average)

MALES

	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
Age	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	30.4	41.3	43.3	31.4	19.6	24.1	41.2	26.1	15.6	22.3	22.6	25.5	9.7	7.2	7.1	17.2	10.3	12.5	20.8	17.0	23.1
30-	35.7	43.0	44.6	33.2	19.7	19.1	42.0	26.0	22.3	31.7	30.6	45.4	10.5	8.1	8.7	19.8	12.4	15.8	24.7	21.0	25.2
40-	44.9	46.8	65.2	37.2	22.6	22.1	48.8	30.4	25.1	47.1	28.6	40.2	12.1	9.5	10.1	28.6	15.3	19.1	32.9	23.6	29.1
50-	61.2	48.5	53.3	46.5	27.0	38.2	59.3	32.3	27.2	90.4	37.5	57.0	14.4	10.8	11.6	45.4	19.3	20.2	52.8	29.5	34.6
60-	93.6	51.9	52.1	60.0	34.8	29.6	85.6	34.4	29.0	149.4	50.2	90.2	17.1	13.4	14.8	63.1	25.5	36.3	80.2	38.4	45.0

FEMALES

	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
Age	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	48.2	43.5	53.6	36.8	20.7	18.3	82.1	26.5	19.9	44.6	25.7	30.7	11.8	7.8	9.2	21.9	15.3	15.1	28.9	18.5	22.0
30-	65.1	48.1	46.4	46.4	22.3	24.9	40.0	26.5	21.0	93.4	25.5	59.5	14.4	11.5	12.4	31.1	18.9	19.1	48.3	24.1	29.6
40-	91.0	59.5	59.4	48.9	28.1	23.8	65.6	36.2	31.3	139.0	38.8	36.5	15.3	13.8	14.4	38.3	22.8	23.3	63.1	28.7	31.0
50-	169.0	52.9	49.7	71.9	37.7	20.9	149.6	38.0	33.8	266.6	38.2	78.6	17.4	14.5	16.6	55.4	27.9	32.0	99.5	33.1	37.5
60-	105.0	52.4	54.6	77.5	36.6	49.0	145.0	27.8	28.0	161.0	50.2	71.6	16.9	20.3	16.2	39.1	34.8	32.2	54.5	39.4	47.8

In recent years the study of 3 major episodes have demonstrated clearly the harmful effect of heavily polluted air. All these incidents took place under unusual climatic conditions in industrialized areas. Firket (1931) reported the result of an investigation into the Meuse Valley incident of December 1930, in which more than 6,000 people became ill and more than 60 died during one week's period of heavily polluted fog. Schrenk et al. (1949) studied a similar episode in Donora, Pennsylvania in October 1948. Here the fog lasted 3 days, and 18 deaths were attributed to it. Firket (1931) in his paper on the Meuse Valley incident, estimated that should an occurrence of similar severity descend on the Thames valley the number of deaths in London would be more than 3 000. The predicted disaster came in December 1952, during a period of fog lasting 4 days. A committee of Departmental Officers and Expert Advisers appointed by the Ministry of Health investigated this episode, and their findings were reported in 1954. It was estimated that about 4,000 deaths could be attributed to the fog, mainly in elderly people already suffering from cardio-respiratory diseases. Regarding morbidity the report concludes that although no comprehensive statistics are available, there appears to have been an increase in morbidity which was, however 'less than might have been expected from the excessive mortality'. The report draws attention to increased mortality in previous fog episodes in London, and Logan (1956) and Bradley, Logan & Martin (1958) have reported on more recent incidents, showing the same association between rise in atmospheric pollution and mortality.

No detailed analysis is available to indicate all the constituents of fog which may have an adverse effect on health. The Commission studying the Meuse Valley incident concluded that sulphur dioxide and sulphuric acid were present in the fog in sufficient quantity to have caused the disaster. Roholm (1937) was of the opinion that fluorine intoxication was the cause. The final conclusion regarding the harmful agents in the Donora episode, was that no single substance was responsible, but that the toxic effects could have been produced by a combination or summation of the action of two or more contaminants, of which sulphur dioxide was probably of significance. The Committee studying the London fog of 1952 concludes that 'on the evidence available it would seem that the oxides of sulphur were the main irritants present, but further investigations are needed on the possible role of other constituents'.

Much less is known about the long-term effect on respiratory morbidity and mortality of exposure to lower concentrations of polluted air over a longer period of time. A number of investigations have strongly indicated that a rather close association may exist. It is surprising, however that scientific studies on the relationship between polluted air and respiratory diseases have not been carried out until recent years, although the general problem of air pollution has been recognized for centuries. In 1306 a Royal Proclamation by Edward I prohibited the use of *sea-coal* in *fire-places* in London (Shaw & Owens 1925). The

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MALES

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Age	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	30.4	41.3	43.3	31.4	19.6	24.1	41.2	26.1	15.6	22.3	22.6	25.5	9.7	7.2	7.1	17.2	10.3	12.5	20.8	17.0	23.1
30-	35.7	43.0	44.6	33.2	19.7	19.1	42.0	26.0	22.3	31.7	30.6	45.4	10.5	8.1	8.7	19.8	12.4	15.8	24.7	21.0	25.2
40-	44.9	46.8	65.2	37.2	22.6	22.1	48.8	30.4	25.1	47.1	28.6	40.2	12.1	9.5	10.1	28.6	15.3	19.1	32.9	23.6	29.1
50-	61.2	48.5	53.3	46.5	27.0	38.2	59.3	32.3	27.2	90.4	37.5	57.0	14.4	10.8	11.6	45.4	19.3	20.2	52.8	29.5	34.6
60-	93.6	51.9	52.1	60.0	34.8	29.6	85.6	34.4	29.0	149.4	50.2	90.2	17.1	13.4	14.8	63.1	25.5	36.3	80.2	38.4	45.0

FEMALES

	Peptic ulcer			Appendicitis			Hernia			Asthma			Influenza			Bronchitis & Pneum.			All diseases		
Age	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B	E&W	O	B
20-	48.2	43.5	53.6	36.8	20.7	18.3	82.1	26.5	19.9	44.6	25.7	30.7	11.8	7.8	9.2	21.9	15.3	15.1	28.9	18.5	22.0
30-	65.1	48.1	46.4	46.4	22.3	24.9	40.0	26.5	21.0	93.4	25.5	59.5	14.4	11.5	12.4	31.1	18.9	19.1	48.3	24.1	29.6
40-	91.0	59.5	59.4	48.9	28.1	23.8	65.6	36.2	31.3	139.0	38.8	36.5	15.3	13.8	14.4	38.3	22.8	23.3	63.1	28.7	31.0
50-	169.0	52.9	49.7	71.9	37.7	20.9	149.6	38.0	33.8	266.6	38.2	78.6	17.4	14.5	16.6	55.4	27.9	32.0	99.5	33.1	37.5
60-	105.0	52.4	54.6	77.5	36.6	49.0	145.0	27.8	28.0	161.0	50.2	71.6	16.9	20.3	16.2	39.1	34.8	32.2	54.5	39.4	47.8

chitis death-rates in County Boroughs and other indices of atmospheric pollution: consumption of coal per acre (1954), and per acre of built up area (1959). In these studies from England & Wales the association was still statistically significant after allowances had been made for other environmental factors al class). This is in agreement with the results obtained by Fairbairn & Reid 8) in a study of the relationship between respiratory mortality and mor y and various environmental factors. Their study covers the whole of the ed Kingdom, and as an index of air pollution they used the results of a ey of visibility made in the winters of 1936-7 and 1937 8, published by rt in 1940 Bronchitis mortality was found to be highly significantly corre-d with the fog index in both sexes, but not to population density or domestic rcrowding. Male pneumonia mortality was found significantly correlated 1 fog and population density but the correlations between female pneumonia tality and these indices were not significant. They found no direct rela ship between pulmonary tuberculosis mortality and fog, but this disease wed a significant relationship in both sexes to domestic overcrowding, and population density Neither male nor female lung cancer death-rates showed relation to fog or domestic overcrowding, but were highly significantly related with population density Sickness absence from bronchitis and pneu-nia in Civil Servants was consistently related to fog, but the association was statistically significant. It was also shown, that among postmen working of doors in areas of high presumptive air pollution, the bronchitis and eumonia absence rate was much higher than among male indoor staff In this dy one can assume that the comparisons made of sickness experience in differ areas are reliable, as the population is uniform with respect to occupational d socio-economic factors.

International data on atmospheric pollution are scarce, as in most countries asurements of air pollution are carried out in a few areas only These areas e usually selected because they have an exceptionally high degree of pollution mpared with the rest of the country It is therefore not possible to make valid sessments on an international scale of the relationship between measurements air pollution and respiratory mortality

It also seems impossible to obtain reliable indirect indices of atmospheric ollution in different countries. To use data on consumption of coal per unit rea in conformity with Daly (1954 1959) seems without validity as the popu-tion density varies enormously from country to country and data for built-up reas in various countries are not available. Further the contamination of the ir is influenced both qualitatively and quantitatively by differences in the ypes of fuel used and the methods of combustion of smoke-producing fuels.

Two papers have been published reporting the results of investigations on ir pollution in Norway Campbell & Kreyberg (1956) measured the atmospheric pollution in central Oslo during 1955 Their results are based on one

effect of air pollution on health was pointed out by Evelyn (1661 reprinted 1930) who states

> And what is all this, but the Hellish and dismal cloud of Sea-Coale? which is not only perpetually imminent over her (London's) head, but so universally mixed with the otherwise wholesome and excellent Aer that her inhabitants breathe nothing but an impure and thick Mist, accompanied with a fuliginous and filthy vapour which renders them obnoxious to a thousand inconveniences, corrupting the Lungs, and disordering the entire habit of their Bodies, so that Catharrs, Phthisicks, Coughs and Consumption, rage more in this one City than in the whole Earth besides.

The striking difference in mortality from respiratory diseases in general, and chronic bronchitis in particular between urban and rural areas, has in the last decades initiated an increasing number of studies designed to throw light on the relationship between atmospheric pollution and respiratory illnesses. The principle of all these studies has been comparisons of population groups in areas with different levels of air pollution. Correlation of mortality and morbidity rates to air pollution have, however certain important limitations

a) The various measurements or indirect indices of air pollution are by nature inaccurate, and little is known about which components in the polluted air have effect on the respiratory tract.
b) Nothing is usually known about the length of time the persons, to whom the morbidity and mortality figures refer have been exposed to the recorded air pollution as migration has not been taken into consideration. Bias may also be introduced by people living in a certain area and spending their working hours in other areas with different degrees of air pollution.
c) As in all correlation studies, a significant correlation between the factors under study may in part, or entirely be due to associated variables.

These reservations have to be taken into account in drawing inferences from such studies.

Haytorn & Heller (1938) studied mortality in a group of industrial towns in the U.S.A. during the 1932 3 economic depression. They found a substantial decrease in mortality from pneumonia during this period of diminished air pollution, although there was a simultaneous decrease in the standard of living in these towns. The decrease in death rates was observed in both males and females, thus diminishing the possibility of occupational factors. Mills's (1952) comparative mortality study between the most polluted and the cleanest areas in Chicago showed the same excess in pneumonia mortality in the heavily polluted areas.

In England & Wales Pemberton & Goldberg (1954) correlated death rates from bronchitis for males and females over 45 years of age in County Boroughs with the average recorded sulphur-dioxide air pollution. They found a significant association in all age-groups in males, but only in the 65 + age-group in females. Daly (1954 1959) found a similar highly significant correlation between bron-

Unfortunately no measurements of atmospheric pollution are available from other parts of Norway. It is quite conceivable that the degree of air pollution in some smaller industrial communities may be higher than in Oslo, but the majority of the Norwegian population is certainly exposed to lower concentrations than those found in the largest city.

TOBACCO-SMOKING

From a number of studies published in recent years it emerges that morbidity as well as mortality from chronic bronchitis and pneumonia are rather closely related to tobacco-smoking, especially the smoking of cigarettes. This relationship has been studied in large prospective studies on mortality among smokers and non-smokers, and by comparing the smoking habits of patients suffering from bronchitis with those of controls. Doll & Hill (1956) studied the mortality experiences among c. 40,000 British doctors on whom detailed information on smoking habits had been obtained prior to last illnesses. They found a statistically significant excess mortality from chronic bronchitis among heavy smokers compared with non-smokers. Light smokers occupied an intermediate position. Hammond & Horn (1958) found significantly higher mortality from pneumonia in smokers than in non-smokers. Their results are based on the mortality experiences of 187,783 males in the U.S.A. Dorn (1959), in a study of mortality among policy-holders of U.S. Government life insurance (mainly veterans from World War I) found that regular cigarette-smokers had an increased risk of dying from a number of respiratory diseases apart from cancer of the lung, i. e. bronchitis, pleurisy and emphysema. The excess mortality among regular cigarette-smokers was higher for heavy than for light smokers. There was no evidence that pipe- and cigar-smokers had an excess mortality from these respiratory diseases, but the numbers in these smoking categories were small. Oswald & Medvei (1955) conclude from a study of respiratory symptoms and bronchitis in 5 844 civil service clerical workers that the over all excess of bronchitis in males in their study population, can be explained entirely by the fact that smoking is much more common in men than in women. Palmer (1954) in a study of hospital patients admitted to the Middlesex Hospital for treatment of hernia and peptic ulcer found that the prevalence of chronic bronchitis was significantly higher in smokers than in non-smokers, and that the prevalence increased with the amount smoked. The same tendency has emerged from a number of field-surveys of respiratory symptoms in populations living in different areas and working in various occupations (Higgins 1957, 1959, Ogilvie & Newell 1947, Fletcher et al. 1959). Higgins et al. (1959) conclude that the influence of tobacco on the prevalence of respiratory symptoms and bronchitis is so important that it is essential to allow for differences in smoking habits in comparable groups before drawing conclusions about the importance of other factors.

sampling station only and considering the substantial local variations found in other investigations on air pollution valid inferences can hardly be drawn from their results. They found that total air contamination, as well as concentration of 3 4 benzpyrene, was at about the same level as in a small rural town in Wales (Llangefni) They also report measurements from a station in Bergen during the winter 1955 and these showed rather similar figures to those in Oslo.

Lindberg & Natvig (1959) have published preliminary results from a dust fall survey in Oslo in 1956-7 using the British Standard Deposit Gauge. Their study refers to 49 sampling stations representing industrial housing and mixed areas in the central, the middle and the peripheral zones of Oslo. The average total dust fall in grams per 100 square metres per 30 days varied from 681 grams in the industrial central areas to 200 grams in the housing areas in the peripheral zone. Studying seasonal variation in dust fall they found a drop in the values in December followed by a peak in April and explained this as due to a reduction of the wind-generated dust during the snow-covered period, followed by an increase when the snow melts leaving the sand and gravel gathered through the winter In this context the authors warn against comparisons of values of dust fall from places with other snow conditions during the winter and suggest that a substantial proportion of the total dust fall in Oslo is composed of road dust. That the atmospheric pollution in Oslo differs quantitatively from that in London, also emerges from a table given in the paper comparing the results from Oslo with those obtained from 40 sampling stations in London in 1955 using the same technique. The table is reproduced in translated form below

It is of particular interest that the concentrations of tar derivates and sulphur are found to be markedly lower in Oslo than in London, as such components of the polluted air have been generally looked upon as those most likely to be harmful to the human respiratory tract.

TABLE 14

ATMOSPHERIC POLLUTION

Dust fall surveys

Average values for Oslo as percentage of average values for the London area

Area	Total dust fall	Ash	Combustible matter	Tarry matter	Sulphate (SO_4
Oslo, central zone	55	57	56	28	41
Oslo, middle zone	44	42	44	22	36
Oslo, peripheral zone	24	20	19	12	21

From Lindberg & Natvig (1959)

subject has so far been carried out. Neither is there any information on which components in cigarette-smoke may have a harmful effect on the respiratory tract, apart from strong suggestions of a carcinogenic effect of 3 4 benzpyrene.

These limitations make it difficult to draw inferences from correlation studies based on the given figures for tobacco consumption in different countries and mortality from various diseases in the same countries.

In Table 15 the rank correlation coefficients are given between cigarette consumption and mortality from different diseases in the same 14 countries for which the mortality data have been discussed in previous sections. The rank correlation method (Kendall 1955) was preferred to the product moment correlation analysis for the following reasons:

a) Ranking will to a certain extent reduce the effect of minor numerical inaccuracies in the measurements of the variables.

b) The relationship will not be unduly affected by extreme values of the variables in any particular country

c) No assumptions have to be made about the distribution of the variables.

Cigarette consumption has been correlated with a number of diseases, apart from the particular conditions under study (bronchitis and pneumonia), in order to test the 'specificity' of any correlation found. The importance of this procedure in this type of correlation studies was clearly demonstrated by Yerushalmy & Hilleboe (1957) in their critical analysis of investigations into the relationship of dietary fat and mortality from coronary disease.

From the table it will be seen that in males there is a statistically significant correlation between the national cigarette consumption in 1935 and mortality from bronchitis and pneumonia (B 31+32) and from respiratory cancer (160-5) 20 years later No significant correlations are found between present cigarette consumption and these diseases. The group 'Total cardiovascular diseases' and its major subgroup 'Arteriosclerotic and degenerative heart diseases' are significantly correlated to both present and past cigarette consumption. No significant correlations are found between cigarette consumption and various other diseases.

Nielsen & Clemmesen (1954) stressed that cancer of the lung may be more closely associated to past than to present cigarette consumption. That this may also be true for chronic bronchitis seems quite conceivable, considering its long chronic course.

The highly significant correlation found between male death-rates from 'bronchitis and pneumonia' and from respiratory cancer makes diagnostic transfers between these groups less probable as an explanation of differences between countries in mortality from 'bronchitis and pneumonia'

No significant correlations are found between cigarette consumption and female death-rates from any cardio-respiratory disease. This is probably due to the fact that the total cigarette consumption in most countries reflects the smoking habits among males. Cigarette-smoking among females is probably in most

These results from epidemiological studies receive some support from experimental data on the effect of cigarette-smoke on the bronchial epithelium.

Leuchtenberger *et al* (1958) exposed mice to cigarette smoke and found that of 23 animals 17 developed 'bronchitis' with damage of the ciliated epithelium of the bronchiae and an increased number of mucus producing elements. No valid inferences can be drawn from results obtained in animal experiments to the possible effect in the human respiratory tract, but it is of interest that the morbid anatomical findings in this study are rather similar to the pathologic features of the bronchial mucosa found by McA Reid (1954) in patients with chronic bronchitis. Chang & Cowdry (1955) in an autopsy study of cigarette-smokers made almost similar findings, and Hilding (1956) found that cigarette-smoke inhibited the ciliary action in the bronchial tubes and thereby interfered with the normal protective mechanism. These experimental observations may suggest that inhaled tobacco-smoke by a) increasing the mucus production, and b) decreasing the ciliary protection may be of significant importance in the causation of early symptoms of chronic bronchitis. This hypothesis seems to deserve testing by planned experiments.

Statistical data on tobacco consumption The most comprehensive data on tobacco consumption in different countries are given in Todd's publication 'Statistics on Smoking (1959) For most of the countries the data cover the last 40 years, for the U K., however yearly consumption figures are given back to 1890 The usefulness of the data for epidemiological purposes is restricted for various reasons, the most important of which are

a) The data refer to total consumption of different tobacco products. No information is given on the type of tobacco (Virginia, Turkish etc.) nor on possible differences between countries and/or time periods in the processes involved in transforming the raw tobacco into different products intended for consumption.
b) Except for the U K. no data are given on the proportions of smokers and smoking habits in different age and sex groups of the total adult population.
c) The data given for different consumption categories (cigarettes, pipe-tobacco) may not reflect the real proportion of cigarette-smokers, as the habit of smoking hand rolled cigarettes varies from country to country In the publication this has been taken into account for 5 countries Australia, Canada, New Zealand, Norway and Portugal and the cigarette consumption in these countries is for the last year covered estimated from the taxation value of cigarette paper in addition to the manufactured cigarettes sold.

This last reservation raises the question of whether hand rolled and manufactured cigarettes are comparable with respect to their possible etiological importance in various diseases. As far as the author knows no investigation on this

subject has so far been carried out. Neither is there any information on which components in cigarette-smoke may have a harmful effect on the respiratory tract, apart from strong suggestions of a carcinogenic effect of 3:4 benzpyrene.

These limitations make it difficult to draw inferences from correlation studies based on the given figures for tobacco consumption in different countries and mortality from various diseases in the same countries.

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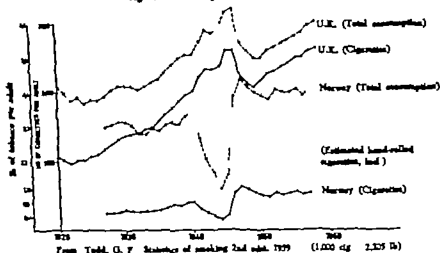


Fig. 22

of the countries under study a relatively recent addiction, for the proportion of smokers in the female populations is comparatively low and the consumption per smoker less than in the males.

Tobacco consumption in England & Wales and Norway Fig. 22 shows the secular trend in tobacco consumption in the two countries, based on the data given by Todd (1959). The total consumption per adult is considerably higher in England & Wales during the whole period covered, and the proportion of cigarettes to the total amount smoked is more than double in England & Wales compared with Norway One has to take into account, however that hand-rolled cigarettes are probably much more common in Norway mainly because of a substantial price difference between tobacco and manufactured cigarettes. Available data from surveys on smoking habits in Norway suggest that the figures given by Todd (1959) are underestimating the true consumption of manufactured and hand rolled cigarettes combined.

Kreyberg, H. J A. (1954) analysed available statistical material on smoking habits in Norway in this century He concludes that the total tobacco consumption per adult remained stable during the four decades preceding World War II but increased to a level approximately one-third above the old during the years after the war The amount of tobacco smoked rather than that used as snuff or for chewing was found to have increased steadily at least since 1928. The relative consumption of cigarettes has increased from about one-third of the tobacco

TABLE 15

Mortality in Relation to Tobacco Consumption and Certain Demographic Factors in 14 Countries

Rank Correlation Analysis

		Rank correlation coefficient	Probability
MALES			
Bronchitis + Pneumonia	▼ cigarette consumption 1935	0.4420	P: *0.0324*
	▼ 1955	0.2088	P: 0.3222
	▼ total tobacco consumption 1935	0.0110	P: 0.9602
	▼ 1955	−0.1090	P: 0.9124
	▼ population density	0.3626	P: 0.0008
	▼ % population in urban areas	0.2564	P: 0.2440
	▼ % population in mining & manufacturing	−0.0770	P: 0.7406
	▼ cancer of resp system	0.5165	P: *0.0117*
	▼ all other cancers	0.1210	P: 0.5824
	▼ total cardiovascular diseases	0.2747	P: 0.1868
	▼ other heart diseases (B 27)	−0.0110	P: 0.9602
	▼ arteriosclerotic heart diseases (B 26)	0.0330	P: 0.9124
	▼ ulcus of duodenum	0.2820	P: 0.2006
	▼ ulcus of stomach	0.3740	P: 0.0472
	▼ diabetes mellitus	0.0110	P: 0.9602
Cancer of resp system	▼ cigarette consumption 1935	0.7293	P: *0.0004*
	▼ 1955	0.3736	P: 0.0702
All other cancers	▼ 1935	0.2200	P: 0.2984
	▼ 1955	0.0110	P: 0.9602
Total cardiovascular diseases	▼ 1935	0.4945	P: *0.0036*
	▼ 1955	0.5604	P: *0.0063*
Arteriosclerotic heart diseases	▼ 1935	0.4286	P: *0.0376*
	▼ 1955	0.5385	P: *0.0081*
Other diseases of heart (B 27)	▼ 1935	−0.1040	P: 0.6672
Ulcus of stomach	▼ 1955	−0.0510	P: 0.8572
Ulcus of duodenum	▼ 1955	0.0000	P:
Diabetes mellitus	▼ 1955	0.0330	P: 0.9324
FEMALES			
Bronchitis + Pneumonia	▼ cigarette consumption 1935	0.0990	P: 0.6600
	▼ 1955	0.0000	P:
	▼ population density	−0.0330	P: 0.9124
	▼ / population in urban areas	−0.1538	P: 0.5028
Male/female ratios B 31+32	▼ 1935	0.3842	P: 0.0688
	▼ male death rates	0.6856	P *0.0009*
	▼ female death rates	0.1284	P 0.5418
Male death rates B 31+32	▼	0.4620	P *0.0244*

Data from: WHO, Ann. Epid. & Vital Stats. 1955 Demographic Year Book 1956, Todd, G F 1959

Time trend in total tobacco consumption and cigarette consumption U.K. and Norway

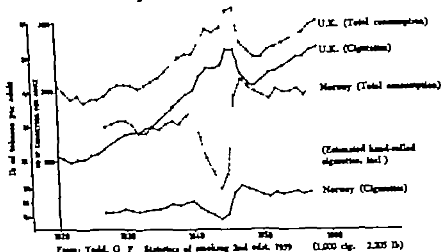


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Sanderud (1958) interviewed the next of kin about the smoking habits of deceased as part of a study of metaplastic changes of the bronchial epithelium in a series of autopsies carried out at the University Clinic in Bergen. This method of obtaining such data on smoking habits has been investigated by Stocks (1957) and found rather unreliable. Furthermore, the autopsy material is for various reasons highly selected. Consequently no inferences can safely be drawn from the data given in this paper to the smoking habits in the general population.

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In Tables 16 a and b, data are given on smoking habits in the adult population in England & Wales, Norway and Denmark. Data from Denmark have been included because the mortality from respiratory diseases in that country is very similar to the Norwegian mortality It is found that the proportion of male smokers is about the same in the three countries. The proportion of cigarette-smokers is substantially higher in England & Wales than in the other countries. Table 16 a shows that the majority of Danish and Norwegian cigarette-smokers consume less than 15 cigarettes per day whereas 54 per cent of British male cigarette-smokers have a consumption of more than 15 cigarettes per day There are smaller differences among the females, but here also the proportion of heavy smokers is higher in England & Wales compared with the other countries. Even if the surveys on which Tables 16 a and 16 b are based, are not strictly compa-

TABLE 16a

Percentage Distribution of Adult Population by Levels of Cigarette Consumption

Grams of tobacco per day	Males			Females		
	E & W	Denmark	Norway	E & W	Denmark	Norway
1–4	6.0	4.7	9.0	10.5	17.6	10.0
5–14	18.9	11.9	23.0	19.4	14.3	9.0
15–24	22.8	5.4	6.0	7.8	0.9	0.0
25+	10.3	1.4	2.0	1.8	0.1	0.0
Total	58.0	23.4	40.0	39.5	32.9	19.0

From England & Wales: Todd, G. F (1959), Denmark: Hansoft, H., Lindhardt, M (1955), Norway Gallup Institute Poll (1959)

TABLE 16b

Percentage Distribution of Adult Male Population by Smoking Habits

Smoking category	E & W	Denmark	Norway
Non-smokers	28.0	22.0	28.0
Pipe	8.0	38.0	20.0
Mixed	9.0	–	24.0
Pure cigarette	55.0	23.0	28.0
Cigars	–	16.0	–
Average cigarette consumption per day per cigarette-smoker	18.4	11.7	9.9*

In the data from Denmark mixed smokers are allocated to the group of highest consumption.

Average all type of tobacco products.

From: England & Wales Todd, G. F (1959), Denmark Hansoft, H., Lindhardt, M. (1955), Norway: Kreyberg, L. (1955)

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OCCUPATION

Many investigations (Pemberton 1956, Higgins *et al.* 1956, 1959) suggest that men in heavy and dusty occupations are more liable to suffer from chronic bronchitis than persons engaged in cleaner work. International comparisons of existing data on occupation are probably of little value, as the working conditions within the same occupational group presumably vary both within and between countries for various reasons. On relating the death-rates from bronchitis and pneumonia to the proportion of adult males occupied in mining and manufacturing in the 14 countries, no significant correlation was found.

SOCIAL CLASS

The large differences in mortality from bronchitis and pneumonia between the different social classes are one striking feature which emerges from the vital statistics (Registrar General's Decennial Supplement 1951) There is a steep gradient of increasing mortality from the higher to the lower social classes. Various environmental factors have been suggested to be involved in the causation of these social class differences: occupation, housing (Stuart Harris & Hanley 1957) diet, medical care (Reid 1958), but it seems difficult to assess the importance of any single factor separately within the multifactorial social class concept. The fact that the male/female ratio remains much the same within each social class, may suggest that occupation *per se* is of minor importance in this context, and that the social class gradient is related to factors affecting the two sexes quite similarly

Mortality data by social class are available in few countries, and it seems very difficult to find any indirect indices of socio-economic environmental conditions in different countries that are valid in relation to death-rates for the total populations. Figures are available on the distribution of income in different countries, but variations in cost of living, and a number of other socio-economic factors would have to be taken into account when using income as an index of social class in comparative studies between countries. Theoretically a useful

figures from Denmark (Hamtoft & Lindhardt 1955) are 61 and 41 per cent, and Nilsen (1959) found in Norwegian school-children 63 per cent male and 48 per cent female smokers in the same age-group

The possible significance of national differences in the length of discarded cigarette-ends, has been discussed in a number of papers in recent years. Doll *et al* (1959) have published the results of an investigation carried out in England, but no comparable study has been undertaken in Norway Reliable data on the consumption of filter tipped cigarettes in the two countries are not known to the author

CLIMATE

Apart from the association of bronchitis and pneumonia with fog in areas with a high degree of air pollution, little is known of the importance of climatic factors in the causation and course of these diseases. As the climatic differences between the different countries under study are not larger than differences within the same country it seems of little value to relate any climatic data to national death rates.

POPULATION DENSITY

Little is known of the possible influence on mortality and morbidity from bronchitis and pneumonia of population density *per se* Population density may however be associated with both a higher degree of atmospheric pollution and with better chances of transfer of respiratory infections which may have some influence on the course of chronic bronchitis.

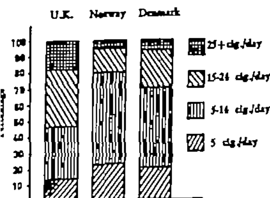


Fig. 24

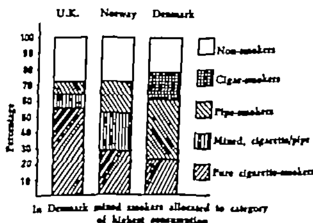


Fig. 23

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index might be obtained by using a method of scoring which takes into account a number of social and economic factors, but there is neither sufficient knowledge as to which factors are of importance nor available numerical measurements of some conceivable factors.

A comparison of these environmental factors (climate, population density occupation) in relation to national death-rates between England & Wales and Norway is likewise invalidated by many factors, of which the following are probably the most important

a) The large climatic differences within Norway overshadow the minor differences between most of England & Wales and the southern and western parts of Norway These districts have the greater part of the total Norwegian population.

b) The enormous difference in the topography of the two countries invalidates completely the usefulness of population density measured as persons per unit of geographical area, for comparative purposes. Neither does it seem valid to use the degree of urbanization as an index of air pollution because of large differences in the type of industries within urban areas in the two countries. Furthermore, in Norway hydroelectric power and oil are the main sources of energy both in industry and in private households, whereas in England & Wales the burning of coal and other solid fuels is the predominant method of energy production.

c) The degree of industrialization is different in the two countries, with 26 4 % and 41.2 % of the working population occupied in mining and manufacturing in Norway and England & Wales respectively in 1954 The geographical distribution of industry differs, with numerous large aggregations of industrial communities in England & Wales and more scattered industrial plants in Norway

Discussion

Geographical pathology has been defined as the comparative study of the incidence of disease and the distribution of physiological trends in peoples belonging to different communities throughout the world and the correlation of these data with features of the social and geographical environments (Study Group, The Council for International Organizations of Medical Sciences 1959) The prime object of the preceding part of the present study is to investigate the usefulness of existing statistical data of various types and from different countries in the study of the geographical pathology of chronic respiratory diseases, and to see whether such data might provide clues for the etiology of these diseases.

In different sections of the paper some of the uncertainties involved in the basic statistical data have been emphasized. With regard to mortality statistics,

it seems justified to say that at their present stage of development they can only provide evidence of real international differences in mortality within rather broad diagnostic groups. Such grouping may admittedly completely conceal existing differences within more specific subgroups. On the other hand, there is a considerable risk of producing fictitious disparities when comparing very restricted diagnostic entities. In either case the epidemiological picture of the diseases under study may be distorted. The limitation of the groups will have to be determined partly by the nature of the diseases studied, and partly by the amount of additional information available from different countries on habits of diagnosis, certification and classification of causes of death.

From the present study it seems justifiable to conclude that marked differences exist in the mortality experience of middle-aged people in a group of economically advanced countries, and that these differences are mainly caused by diseases of the cardio-respiratory system. There are strong suggestions that real disparities also exist in some more restricted groups, for example bronchitis and pneumonia, but this cannot be established conclusively from the data available.

In comparing England & Wales and Norway it has been possible to take into account relevant additional information, and it emerges that there is a substantial excess mortality in England & Wales from cardio-respiratory diseases in general and from a number of more specific subgroups. With regard to morbidity the comparability of the available data is, as pointed out previously probably more restricted. There is a strong suggestion, however that real differences also exist in morbidity measured as spells of illnesses for bronchitis and pneumonia, but these are not as marked as for mortality This disparity between the difference in mortality and morbidity may be caused by the observed differences in the degree of atmospheric pollution in the two countries. This hypothesis is consistent with Higgin's (1957) observation that the prevalence of respiratory symptoms was rather similar in two areas with a marked difference in air pollution, whereas the mortality rates were significantly higher in the most polluted area. The aggravating effect of air pollution on established respiratory disease was also demonstrated by Reid & Fairbairn (1958) in their follow-up study of postmen invalided owing to chronic bronchitis.

The consistent male excess mortality from most cardio-respiratory diseases in the countries under study suggests that similar etiological factors, to which males are either more exposed or more susceptible may universally determine the prevalence of these diseases. The differences observed between countries could be explained by differences in the degree of exposure to these factors. This hypothesis is supported by the finding of a statistically highly significant positive correlation between the male death-rates from bronchitis and pneumonia and cigarette consumption 20 years previously The validity of using the available consumption data as an estimation of male smoking habits is strengthened by

the highly significant correlation found between these data and mortality from cancer of the respiratory system, a disease entity in which the association with smoking has been established conclusively in a number of extensive studies. The positive correlation between the mortality from bronchitis and pneumonia and respiratory cancer may also indicate common etiological factors, and this assumption is supported by the similarity in the time trends of the male/female ratio of the two disease groups in England & Wales. It seems more likely that this remarkable similarity in time trends is due to common factors, rather than to coincidence in time of different factors producing almost identical sex-differentials.

It is difficult to see how atmospheric pollution can account for the increasing male/female ratio in respiratory disease which can de observed from the 1920-30 decade onwards in England & Wales. If anything, the degree of air pollution is less now than in the first decades of this century The composition of pollution has probably changed due to the increase of combustion products from automobiles and other motor vehicles, but there is no indication that this qualitative difference is of decisive importance to respiratory diseases. Further the sex difference in exposure to general air pollution is probably rather small and the local atmospheric pollution in factories and other places of work has also decreased in this century due to better industrial hygiene. Changes that have taken place in environmental hygiene, nutrition, standard of living and medical care, have also probably affected the two sexes rather similarly The secular trend of cigarette consumption shows a substantial increase from the first decade of this century onwards, and at least until World War II cigarette-smoking was a predominantly male addiction. If cigarette-smoking is one of the main factors determining the excess male mortality from various respiratory and cardiac diseases, one would expect that the time trends of male cigarette consumption and the male/female ratios would show a certain degree of parallelism. These trends are shown in Fig. 25 for England & Wales (the only country for which all data are available) For the three respiratory categories, the male/female ratios refer to the 5-year group 55—59 years, which shows the maximum sex differential. The trends, however are similar for all age-groups between 45 and 64 For arteriosclerotic heart diseases, the trend is shown for the broad age-group 25-44 years. All respiratory diseases show a definite parallelism with cigarette consumption most marked for respiratory cancer The curves suggest an 'incubation period of 10-20 years for the excess mortality to become manifest. For the given age-group a definite trend also emerges in coronary diseases. In older age-groups, however the male/female ratio of coronary diseases shows little parallelism with cigarette consumption. This is in accordance with the findings of English *et al* (1940) Hammond & Horn (1958) and Doll & Hill (1956) that the association between tobacco consumption and coronary mortality is most marked in younger age-groups.

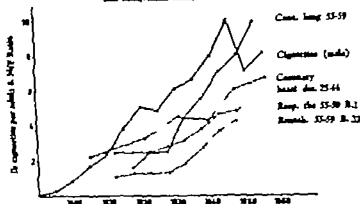


Fig. 23

Considering the increasing amount of epidemiological evidence linking mortality from a number of respiratory diseases and cigarette-smoking, one can hardly avoid the conclusion that smoking may be an important factor determining the observed sex-differences in mortality. *This does not imply* that smoking is the only factor involved in the evolution of respiratory diseases such as bronchitis and pneumonia, nor that the association between these diseases and smoking is as close as that between cigarette-smoking and cancer of the lung. In Norway for example, there has been a consistent increase in the male/female ratio from respiratory cancer in the last two *decades, whereas no similar trend* can be observed for bronchitis and pneumonia.

This assumed variation in the closeness of association between a particular disease entity and one of several etiological factors, may account for the fact that in this study no statistically significant correlations were found between *cigarette-smoking and a number of diseases which in other investigations* have been found associated with smoking, for example respiratory tuberculosis (Lowe 1956, Tinker 1959) and peptic ulcer (Hammond & Horn 1954 Doll & Hill 1956). All these studies were based on more accurate smoking histories, and this *might increase the possibilities of establishing less close — but nevertheless statistically significant — associations, not detectable from the rather* crude data on national consumption.

The finding of a significant correlation between male mortality from arteriosclerotic and degenerative heart diseases and present cigarette consumption, is consistent with the results obtained in a number of studies published in recent years (Hammond & Horn 1958 Doll & Hill 1956, *Dorn 1959 Buechley et al.* 1958). The correlation also found with cigarette consumption 20 years ago, may

suggest that in this disease group past as well as present smoking habits may be of importance.

Berkson (1958) in an appreciation of the papers by Hammond & Horn and Doll & Hill argued that there could hardly be any causal relationship between smoking and lung cancer as increased mortality from a number of other diseases was also found in smokers compared with non smokers. Hammond (1958), among others, has in this context pointed out that it is a well-established biological phenomenon that a single agent may cause a multitude of clinical diseases. Considering that tobacco-smoke is a very complex mixture of a number of organic and inorganic substances, it seems quite conceivable that it may produce a wide variety of pathological conditions. It remains to be established, however which of the many components in tobacco-smoke may be harmful either alone or in interaction with other disease-producing agents, and by which mechanisms they may act on the different tissues and organs involved in various diseases. The possibility of age- and sex-differences in susceptibility' and the time of exposure necessary to produce detectable effects also call for further studies. From existing epidemiological data there are, however strong suggestions that a combined effect of cigarette-smoking and atmospheric pollution to a great extent determines the evolution and outcome of a number of respiratory diseases — particularly 'bronchitis and pneumonia — in middle-aged persons.

Summary and conclusions (Part I)

A critical analysis of available mortality statistics from a number of countries has been carried out in order to try to elucidate some features in the epidemiology of chronic non specific respiratory diseases. The study is confined to the 40-64-year age-group. It is found that the differences between these countries in total disease mortality are mainly caused by differences in the mortality from cardio-respiratory diseases. This seems to reflect real disparities rather than statistical artifacts' In all the countries there is a male excess in mortality from cardio-respiratory diseases, while the female mortality from these causes varies little from country to country

A more detailed analysis has been carried out for the two countries, i. e. England & Wales and Norway showing the extreme values in male cardio-respiratory mortality It emerges that diagnostic transfers between groups of causes of death cannot explain the large differences found in recorded mortality from most cardio-respiratory diseases. In the group 'bronchitis and pneumonia the difference increases with advancing age from a ratio of 5 1 in the 40-44 year age-group to 10 1 in the 55 59 year age-group in males. The ratio falls in higher age-groups. The same feature is also demonstrated by the female rates, but is less marked.

The time trends in the male/female mortality ratios for bronchitis and pneumonia, cancer of the lung and respiratory tuberculosis are very similar in England & Wales, characterized by an increasing ratio in middle-aged persons from the 1920-9 decade onwards. The same feature is found in Norway for respiratory cancer and respiratory tuberculosis, but the change takes place in the 1940-9 decade.

A study of available morbidity data from England & Wales and Norway also suggests a real difference in morbidity from bronchitis and pneumonia, but considerably less than for mortality. This may indicate that non-specific respiratory diseases in England & Wales run a more serious course with a higher fatality rate.

A number of studies link bronchitis and pneumonia mortality and morbidity to certain environmental factors, in particular atmospheric pollution and cigarette-smoking. The difficulties involved in international comparison of the various environmental factors are discussed. Rank correlation studies give some limited support to the hypothesis that cigarette-smoking is a contributory factor in the evolution of chronic non-specific respiratory diseases. Correlation of mortality figures from different countries and existing data on air pollution, population density, degree of urbanization and industrialization, and different indices of the standard of living have been discussed and found to be without validity. To conclude, it seems justified to say that at present, the type of statistical data presented in this study on an international basis can prove few hypotheses conclusively, but can provide some support to results obtained in more restricted investigations, and do point out some features deserving attention in future research in this field.

II

A Field survey of Respiratory Symptoms and Related Factors in England & Wales and Norway

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INTRODUCTION

From the study of available vital statistics it emerges that substantial real differences exist in morbidity and mortality from chronic non-specific respiratory diseases in England & Wales and Norway Considering what is known regarding the evolution of this chronic condition, this feature may imply either that a similar disparity also exists in the prevalence of early' respiratory symptoms, or that the rate of transition from minor respiratory abnormalities to chronic disabling disease differs in the two countries. Both from the point of view of pathogenesis and of preventive medicine it seems of importance to try to decide which of the two alternatives is the more likely explanation for the differences observed in the vital statistical rates. The successful application of preventive measures depends not only on the recognition of diseases in their early phases, but also on knowledge of factors initiating disease and/or aggravating its course. It was therefore decided to carry out field surveys in population groups in England & Wales and Norway in order to try to elucidate the following problems

1 Do real differences exist in the prevalence of respiratory symptoms of varying severity and in respiratory functions?
2. Can dissimilarities in personal habits, environment, past medical history or anthropometry explain differences that might exist?

An accurate estimate of the prevalence of symptoms in a particular community can only be determined by examination of the whole community or of some sample which is representative of it. The corollary to this is that to estimate the difference in prevalence of symptoms between two countries, one would either have to examine the total populations of these countries, or large random samples drawn from these populations. None of these methods is applicable to the study of respiratory symptoms because of the amount of work involved in the examination of each person. A still more serious handicap in using large samples of the general population in this type of investigation, is the poor response rates one often obtains by this method. It seems obvious that under such circumstances the results may be materially biased by the proportion of non respondents This drawback was stressed by Hill (1951) who in this context remarked I would

therefore myself infinitely sooner have, say a one in four sample of the population, of a size thereby which enables me to pursue relentlessly and complete the records for all or nearly all the persons in it, than have to interpret the figures derived from a survey of the "whole" population from which finally a quarter was missing.

In a number of studies published in the last few years it has been shown, however that it is possible to throw light on a number of important features in the epidemiology of chronic respiratory diseases, by investigating relatively small samples selected on a more restricted basis, i. e. from different smaller geographical areas, from different occupations, from limited age-groups. Admittedly these studies of selected groups do not allow inferences to be drawn to prevalence of disease and/or symptoms in a larger community for example, in the general population in a whole country On the other hand one can hope to be able to obtain a high response rate, allowing more reliable conclusions to be drawn from any significant finding. Another advantage of this design is that one can usually standardize' some variables to a certain extent at the planning stage, a procedure that may simplify both the actual field-work and the evaluation of its results.

PREVIOUS INVESTIGATIONS

The results from a number of studies on the prevalence of various respiratory symptoms and chronic bronchitis in different population groups in the United Kingdom have been published in the last few years. So far however only one paper has been published giving the results of investigations carried out in different countries using methods sufficiently similar to justify comparisons. Olsen & Gilson (1960) surveyed a representative sample of men aged 55-64 in Rønne, Bornholm (Denmark), using a standardized questionnaire and measuring ventilatory capacity Their results refer to 183 persons, or 91.5 per cent of the selected sample. All interviews were carried out by the same doctor and the other doctor made the measurements of ventilatory capacity The results obtained are compared with those of Higgins (1957) and Higgins & Cochran (1958) from surveys in rural districts in South Wales and Scotland, using essentially the same questionnaire. A striking similarity in prevalence of respiratory symptoms in the two districts in the United Kingdom was observed and commented on by Higgins & Cochran (1958). The main results of the comparisons between the Danish and the British samples are summarized by the authors as follows: "The prevalence of symptoms is significantly lower in Rønne. The mean indirect maximum breathing capacity (IMBC) is significantly higher in Rønne (106 litre/min.) than in the U.K. samples (92 litre/min.). The questionnaire used also recorded smoking habits, and it was found that there were more non-smokers in Rønne

and many fewer cigarette-smokers than in the U.K. samples. Atmospheric pollution, social and economic factors, height and weight and density of population are also discussed by the authors, who conclude that the differences observed in respiratory symptoms are not explicable on the basis of difference in these factors. Disparity in smoking habits are suggested as a possible explanation, and it is of particular interest that in the small group of non-smokers no physiological or clinical differences were found between the samples

OWN INVESTIGATIONS

The investigation was designed to compare the prevalence for respiratory symptoms and respiratory morbidity in comparable samples of male workers in England & Wales and Norway

Material and methods

CHOICE OF POPULATION

Considering the epidemiological feature of chronic bronchitis it was decided to select samples for study according to the following principles.

a) The study is restricted to males aged 40-64 years.
b) The samples must be without any known special occupational hazards.
c) The samples must be as identical as possible with respect to occupation, social class and income.
d) The groups must be covered by the same type of sickness insurance schemes, and reliable sickness absence records must be available for at least the last 3 years.
e) The groups must be as contrasting as possible with respect to exposure to general atmospheric pollution.
f) The groups must not be liable to a high proportion of refusals or abstainers.
g) The groups must be readily accessible.

After considering various occupational groups, it was decided to study workers in the municipal transport system in Bergen, Norway and transport workers in Post Office Service in London. In Bergen all workers in the transport system aged 40-64 were included in the sample, in London all mail van drivers administratively belonging to one garage in central London were selected for study

As will be seen from Table 17 the Bergen sample includes not only drivers of motor vehicles but also tram-drivers, conductors and maintenance-workers. In order to determine whether any major differences might exist between drivers and others' in the Bergen sample, the two groups have been compared.

The results are given in Table 18. There are no significant differences between the two subsamples, and the total sample has therefore been used in the following analysis and comparisons.

The main reason for not choosing workers in the London Transport Executive for this study was that their sickness insurance schemes differed very much from the scheme covering the selected Norwegian group. Based on Fletcher's (1959) findings it was assumed that this difference might be of much greater importance in determining the respiratory morbidity measured as sickness absence, than any possible effect of a comparatively minor occupational disparity between the samples.

TABLE 17

Sample of Men in Bergen Transport

Age	40-49	50-59	40-59
Actual job	No.	No.	No.
Conductors	22	11	33
Bus-drivers	42	8	50
Tram-drivers	9	22	31
Maintenance-workers	40	38	78
Total population	113	79	192
Refused	—	2	2
Long-term illness	1	—	1
Total in sample	*112*	*77*	*189*

Sample of Men in Post Office Service in London

Age	40-49	50-59	40-59
Total population	74	84	158
Refused	1	2	3
Long-term illness	2	—	2
Total examined	71	82	153
Excluded after examination	2	1	3
Total in sample	69	81	150

Response-rates Bergen $\frac{189 \times 100}{192}$ 98.4 %

London $\frac{150 \times 100}{155}$ 96.8 %

It was unfortunately not possible to use Post Office drivers as study population in Bergen, as this occupational group was too small. In both the samples studied, the workers have their full salary paid during certified sickness absence not exceeding 6 months.

During the analysis of the data it was decided to exclude from the comparative study the age-group 60-64 years. This was done as it became obvious that the men in this age-group in both samples were highly selected compared with the men aged 40-59 due to the rules for retirement and pension. Also, the numbers in this age-group were too small to allow any valid comparisons to be made.

The question of differences between the two countries in the selection of men

TABLE 18

Comparison of subgroups in the Bergen sample

Age	40-49		50-59	
	Tr %	M %	Tr %	M %
Cough on rising winter	26.4	30.0	41.0	39.5
on rising summer	23.6	22.5	38.5	39.5
all day winter	11.1	12.5	20.5	15.8
all day summer	11.1	10.0	20.5	15.8
Phlegm on rising winter	18.1	20.0	33.3	28.9
on rising summer	13.9	17.5	30.8	28.9
all day winter	8.3	7.5	10.3	13.2
all day summer	8.3	7.5	10.3	13.2
Dyspnoea gr II	5.6	0.0	21.1	8.0
gr III & IV	1.4	0.0	10.3	5.3
Wheezing occasionally	38.9	35.0	43.6	44.7
" most days or nights	4.2	10.0	5.1	13.2
Chest affected by weather	18.1	25.0	22.0	34.2
illnesses last 3 years	15.3	12.5	15.4	15.8
Non-smokers	8.3	7.5	2.6	0.0
Ex-smokers	9.7	10.0	5.1	18.4
1-14 g/day	66.7	60.0	76.9	63.2
15-24 g/day	12.5	20.0	15.4	18.4
25+ g/day	2.8	2.5	0.0	0.0
Mean PRF (litres/min.)	326.8	329.4	497.6	506.6

into the occupational groups studied, has not been investigated in any detail. This factor may be of importance in this type of comparative study, but for the occupational group with which we are concerned in this particular investigation, it seems very difficult to find any reliable indices by which this factor can be assessed in relation to the disease entity under study. From Table 19, which gives the time employed in the present job, it will be seen that the average time in present employment is higher in the Norwegian than in the British sample. Most men in the British sample, however, had been employed in driving most of their working life.

No data on income have been collected for any of the samples. This was omitted because it was assumed that even if it was possible to obtain such data they would not provide a valid estimate of the person's standard of living. The living standard in modern urban communities, with a substantial proportion of married women in paid employment outside their homes, is probably more dependent on the family income than on the income of the traditional male 'bread winner'. Compared with other occupational groups, the wages of the men in the two samples are on an average a little lower than the average for the male industrial population in the two countries.

TABLE 19

Comparison of some Characteristics of the Samples from London and Bergen

	London				Bergen			
Age	40-	45-	50-	55-	40-	45-	50-	55-
	No. 27	No. 42	No. 49	No. 32	No. 75	No. 37	No. 34	No. 43
Mean age (years)	41.9	47.3	52.3	56.0	41.6	47.1	52.0	57.1
Mean standing-height (cm)	172.4	171.4	171.5	171.9				
Mean sitting-height (cm)	89.0	87.3	88.0	87.4	91.7	90.2	89.7	88.9
Weight (kg)	74.4	70.7	74.6	66.8	73.2	71.7	70.9	69.3
Time in present employment (years)	7.4	6.5	6.8	7.5	12.5	16.8	21.6	27.0
Previous dusty occupation (No.)	3	4	2	2	3	0	2	2
Born outside London (No.) M.B.	2	2	9	2				
C.B.	3	1	1	3				
U.D.	1	1	1	3				
R.D.	1	1	1	1				
Born outside Bergen (No.) Urban					3	0	0	3
Rural					11	4	4	13
Blood pressure (systolic above 160 and/or diastolic over 95 mm) (No.)	1	2	2	3	3	2	3	7
Abnormal chest X-ray (No.)					5	4	6	11
Abnormal ECG (No.)	1	5	8	14				
Age started regular smoking	17.4	16.7	16.8	16.1	17.8	21.0	20.7	18.9

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all day summer	8.3	7.5	10.3	13.2
Dyspnoea gr II	5.6	0.0	21.1	8.0
gr III & IV	1.4	0.0	10.3	5.3
Wheezing occasionally	38.9	35.0	43.6	44.7
most days or nights	4.2	10.0	5.1	13.2
Chest affected by weather	18.1	25.0	22.0	34.2
illnesses last 3 years	15.3	12.5	15.4	15.8
Non-smokers	8.3	7.5	2.6	0.0
Ex-smokers	9.7	10.0	5.1	18.4
1-14 g/day	66.7	60.0	76.9	63.2
15-24 g/day	12.5	20.0	15.4	18.4
25+ g/day	2.8	2.5	0.0	0.0
Mean PRF (litres/min.)	526.8	529.4	497.6	506.6

into the occupational groups studied, has not been investigated in any detail. This factor may be of importance in this type of comparative study but for the occupational group with which we are concerned in this particular investigation, it seems very difficult to find any reliable indices by which this factor can be assessed in relation to the disease entity under study. From Table 19 which gives the time employed in the present job it will be seen that the average time in present employment is higher in the Norwegian than in the British sample. Most men in the British sample, however had been employed in driving most of their working life.

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Mean age (years)	41.9	47.3	52.3	56.0	41.6	47.1	52.0	57.1
Mean standing-height (cm)	172.4	171.4	171.5	171.9				
Mean sitting-height (cm)	89.0	87.3	88.0	87.4	91.7	90.2	89.7	88.9
Weight (kg)	74.4	70.7	74.6	66.8	73.2	71.7	70.9	69.3
Time in present employment (years)	7.4	6.5	6.8	7.3	12.5	16.8	21.6	27.0
Previous dusty occupation (No.)	3	4	2	2	3	0	2	2
Born outside London (No.) M. B.	2	2	9	2				
C. B.	3	1	1	3				
U. D.	1	1	1	3				
R. D.	1	1	1	1				
Born outside Bergen (No.) Urban					3	0	0	3
Rural					11	4	4	13
Blood pressure (systolic above 160 and/or diastolic over 95 mm) (No.)	1	2	2	3	3	2	3	7
Abnormal chest X-ray (No.)					5	4	6	11
Abnormal ECG (No.)	1	5	8	14				
Age started regular smoking	17.4	16.7	16.8	16.1	17.8	21.0	20.7	18.9

From Table 19 it is found that nearly all the men in the British sample are living within the London Metropolitan Boroughs (mainly the eastern districts), and all men in the Norwegian sample are living within Bergen city Due to practical difficulties no investigation of the actual housing conditions for the men in the two samples has been carried out.

The men in the London sample are, during their working hours, driving mail-vans all over the central part of London. The drivers and conductors in the Bergen sample spend their working hours driving all over the city of Bergen. The rest of the men in the Norwegian sample are partly working in garages and partly engaged in outdoor maintenance work. The indoor workers are only on very rare occasions exposed to exhaust or diesel fumes.

Information on previous exposure to gases and chemical fumes was asked for during the interviews. The reliability of the information obtained may be doubtful, as the degree of exposure will always be a subjective assessment by the individual. It was found impossible in this type of survey to go into any detail on the actual working conditions in each man s previous employments. The same reservation probably also applies to the information obtained on previous exposure to dust, even if particular jobs in certain industries can be classified in broad groups according to risk of dust exposure. From Table 19 it will be seen that a higher proportion of the men in the British sample than in the Norwegian sample had previously been engaged in jobs that can be classified as dusty or probably dusty In most cases, however the exposure to dust took place many years ago

TABLE 20

Meteorological Conditions in Bergen and London (Kew)

	Temp. (F)		Rainfall (mm)		Abs. humidity		Rel. humidity	
	L	B	L	B	L	B	L	B
January	39.7	35 1	50	221	5.2	4.3	85	80
February	40.3	35.0	39	150	5.3	4.2	82	77
March	42.8	37 0	39	141	5.5	4 4	79	74
April	47.5	42.3	43	111	6.2	5 1	75	72
May	53.8	48.6	44	106	7.7	6.6	73	74
June	59 4	53.6	50	103	9 4	8.2	73	77
July	62.7	57.5	60	109	10.5	9.8	73	80
August	61.8	56.3	57	183	10.5	9.7	76	84
September	57 4	52.0	51	199	9 4	8.1	80	83
October	50.3	45.5	64	220	7.8	6.4	85	81
November	44.2	39 4	59	195	6.3	5.0	86	79
December	40.7	36.5	55	206	5.5	4.5	86	79

PLACE OF STUDY

Bergen is situated on the west coast of Norway at 60° 23 North, and 5° 27 East. Low mountains and a chain of small islands protect the city from the North Sea. The climate is moist and mild, (see Table 20), and the prevailing wind-directions are west and south west.

The population in recent years has shown a slow increase. In 1956 Bergen had 114,571 inhabitants.

The traditional basic industries of Bergen are shipping and foreign trade, particularly export of fish and fish products. It has steadily increasing manufacturing industries, and is the commercial and administrative centre of the surrounding part of the country.

No measurements on air pollution are available from Bergen apart from the measurements on 3 4 benzpyrene referred to in part I of this study. As hydro-electric power and mineral oil are the main sources of energy in the industry and in private households, the degree of atmospheric pollution is very low. Fog is rare, and lasts only for a few hours on nearly all occasions.

In Table 20 are given certain meteorological data for Bergen and London.

PROCEDURE

The survey of the Norwegian sample was carried out in September-October 1959 of the British sample in June 1960. The following procedure was applied to each person

1. A standardized interview on respiratory symptoms, past medical history smoking habits and certain occupational factors.
2. Measurements were made of weight, sitting height, (stem height), blood pressure and peak respiratory flow (PRF)
3. Morning sputum specimens were collected.
4. Sickness absence data were extracted from each man's absence record.

All interviews, except three in the British sample, were carried out by the author in order to eliminate the 'between observers variation. To secure a certain degree of comparability between this study and previous investigations in which essentially the same questionnaire had been used, 20-30 test interviews' were carried out on volunteers before the actual field-investigation was undertaken. Most of these volunteers had a number of the symptoms referred to in the questionnaire. The test interviews were tape-recorded, and later played back and discussed with doctors experienced in the use of this particular questionnaire.

In the investigation of the British sample the 'long' questionnaire on respiratory symptoms approved by the Medical Research Council's Committee on the

Aetiology of Chronic Bronchitis (1960) was used. As this questionnaire was not drafted in its final form at the time the field work was done in Norway an earlier version of it had to be used in the Norwegian survey. The wording and the sequence of the questions were, however, for the most part identical in the two versions, and apart from one particular question referred to later, it seems unlikely that these minor differences will affect the results to the extent that comparisons between the two samples would be invalidated. The reason for using the latest approved version in the British part of the study was that the results presented in this study were part of an investigation on cardio-respiratory diseases planned to be carried out in a larger population in London. For the Norwegian part of the study the questionnaire was translated into Norwegian by the author in consultation with Norwegian colleagues.

The Peak Respiratory Flow (PRF) was measured, using the vane type of recorder developed by Wright & McKerrow (1959). The same instrument was used in the whole Norwegian survey and also for about half of the British sample. Due to mechanical breakdown of this particular instrument, it was necessary to use another identical instrument in the later part of the survey in London. The calibration of the two instruments and also the stability of the calibration of each instrument during the survey period, were checked by recording the author's peak respiratory flow. This is obviously not a very satisfactory method of calibration, but it was the only method practical during the survey. Assessed by this method, there was practically no difference between the two instruments used, and the calibration of each instrument was stable during the survey periods. The instructions for using the instruments were given to each person by the author. Five readings were recorded on each subject, except in the very few cases in which the persons became too exhausted to manage to perform 5 consecutive measurements. The average of the last 3 readings was finally recorded as the subject's peak respiratory flow.

Weight (in the Norwegian sample to the nearest 0.5 kg, in the British sample to the nearest lb) and sitting height (in both samples to the nearest cm below) were measured. In the Norwegian sample the measurements were carried out by the same trained nurse, in the British sample by the author except for a few subjects measured by another doctor.

The systolic and diastolic blood pressures were measured, using a standard Hg-manometer. The results were read to the nearest 2 mm below and the point of muffling of the sound was recorded as the diastolic pressure. In the Norwegian sample all measurements were carried out by the author, in the British sample by two experienced doctors.

Morning sputum specimens were collected, using the technique suggested by Elmes *et al.* (1959). The subjects were given small glass containers and asked to expectorate into it all phlegm produced from the chest during the first hour after getting out of bed the following day. The volume and appearance of the

sputum were recorded without opening the containers. Assuming that the containers were uniform in shape, the volume of sputum was calculated from the measurement of the height of the sputum in the vessel and the area of the bottom of the container (This area was calculated from the average diameter of 20 containers measured.)

Sickness absence data in the Bergen sample were extracted from the men's records by the author In the London sample this extraction was done by a clerical assistant trained in this type of work. The diagnostic data extracted were classified according to the International Classification of Diseases (1948).

For the Norwegian sample the results of chest X ray examinations during the last two years were available. No corresponding data were available for the British sample. Electrocardiograms (11 leads) were recorded in the London sample as part of a more comprehensive cardio-respiratory investigation. The ECGs were read and classified by an experienced doctor

Results

PREVALENCE OF RESPIRATORY SYMPTOMS

Table 21 a shows the prevalence of respiratory symptoms in the two samples. In both of the samples it is found that the prevalence of symptoms increases with age, and for most of the symptoms this age-effect is proportionately the same in the two samples.

Cough and phlegm. About one-third of the men in both samples had morning cough lasting for 3 months or more each winter and between a quarter and one-third admitted to the same symptom in the summer As one would expect, cough was more commonly experienced on rising than during the day In both 10-year age-groups the prevalence of morning cough is very similar in the two countries. Cough during the day in the winter shows for both age-groups a higher prevalence in London, whereas there is little difference between the samples in the prevalence of this symptom in the summer

For all questions on phlegm production a higher prevalence is found in the London sample, and the differences from the Norwegian sample are of the same order in the 40–49 and the 50–59-year age-groups. The difference between the countries is most pronounced for phlegm production during the day in the winter

Most of the cough and phlegm recorded could be regarded as chronic. Of the men admitting to cough and/or phlegm lasting for 3 months or more, only 10 per cent in the London sample and 3 per cent in the Bergen sample said that symptoms had been present for less than 3 years.

Aetiology of Chronic Bronchitis (1960) was used. As this questionnaire was not drafted in its final form at the time the field work was done in Norway an earlier version of it had to be used in the Norwegian survey The wording and the sequence of the questions were, however for the most part identical in the two versions, and apart from one particular question referred to later is seems unlikely that these minor differences will affect the results to the extent that comparisons between the two samples would be invalidated The reason for using the latest' approved version in the British part of the study was that the results presented in this study were part of an investigation on cardio-respiratory diseases planned to be carried out in a larger population in London For the Norwegian part of the study the questionnaire was translated into Norwegian by the author in consultation with Norwegian colleagues.

The Peak Respiratory Flow (PRF) was measured, using the vane type of recorder developed by Wright & McKerrow (1959). The same instrument was used in the whole Norwegian survey and also for about half of the British sample. Due to mechanical breakdown of this particular instrument, it was necessary to use another identical instrument in the later part of the survey in London. The calibration of the two instruments and also the stability of the calibration of each instrument during the survey period, were checked by recording the author's peak respiratory flow This is obviously not a very satisfactory method of calibration but it was the only method practical during the survey Assessed by this method, there was practically no difference between the two instruments used, and the calibration of each instrument was stable during the survey periods. The instructions for using the instruments were given to each person by the author Five readings were recorded on each subject, except in the very few cases in which the persons became too exhausted to manage to perform 5 consecutive measurements. The average of the last 3 readings was finally recorded as the subject's peak respiratory flow

Weight (in the Norwegian sample to the nearest 0.5 kg, in the British sample to the nearest lb) and sitting height (in both samples to the nearest cm below) were measured. In the Norwegian sample the measurements were carried out by the same trained nurse, in the British sample by the author except for a few subjects measured by another doctor

The systolic and diastolic blood pressures were measured, using a standard Hg manometer The results were read to the nearest 2 mm below and the point of muffling of the sound was recorded as the diastolic pressure. In the Norwegian sample all measurements were carried out by the author in the British sample by two experienced doctors.

Morning sputum specimens were collected, using the technique suggested by Elmes *et al* (1959) The subjects were given small glass containers and asked to expectorate into it all phlegm produced from the chest during the first hour after getting out of bed the following day The volume and appearance of the

Question	London				Bergen				London		Bergen	
Age	40-49		50-59		40-49		50-59		40-59		40-59	
	No. 69		No. 81		No. 112		No. 77		No. 150		No. 189	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
11a. Have you had this cough/phlegm less than 2 years?	3	4.35	5	6.17	0	–	3	3.90	8	[illegible]	2	[illegible]
11b. Have you had this cough/phlegm 2 years or more?	26	37.68	41	50.62	41	36.61	32	[illegible]	67	[illegible]	73	[illegible]
12b. In the past 3 years have you had period of (increased) cough and phlegm lasting for 3 weeks or more? Only one period.	6	8.70	7	8.64	10	8.93	8	[illegible]	13	[illegible]	18	[illegible]
12c. I the past 3 years have you had period of (increased) cough and phlegm lasting for 3 weeks or more? 2 or more periods.	8	11.59	6	7.41	4	3.57	7	[illegible]	14	[illegible]	11	[illegible]
13b. Have you ever coughed up blood? Streaks.	1	1.45	3	3.70	1	0.89	3	[illegible]	4	[illegible]	4	[illegible]
13c. Have you ever coughed up blood? More.	4	5.80	2	2.47	0		1	[illegible]	6	[illegible]	1	[illegible]
14a. Are you ever troubled by shortness of breath when hurrying on the level or walking p slight hill? (Dyspnoea gr II)	34	49.28	47	58.02	4	3.57	12	[illegible]	81	[illegible]	16	[illegible]
14b. Do you get short of breath when walking with other people at an ordinary pace on the level? (Dyspnoea gr III)	3	4.35	7	8.64	1	0.89	6	7.79	10	[illegible]	7	[illegible]
14c+d. Do you have to stop for breath when walking at your own pace on the level? Are you short of breath on washing or dressing? (Dyspnoea gr. IV V.)	1	1.45	1	1.23	1	0.89	0	–	2	[illegible]	1	[illegible]
15a. Wheezing. Do you get this with colds?	15	21.74	11	13.58	26	23.21	23	29.87	26	[illegible]	49	[illegible]

Table 21 (cont.)

TABLE 21a

Prevalence of respiratory symptoms

Male 40-59 years. Bergen and London

Question	London				Bergen				London		Bergen	
	Age 40-49		50-59		40-49		50-59		40-59		40-59	
	No. 69		No. 81		No. 112		No. 77		No. 150		No. 189	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1 Do you usually cough first thing in the morning in winter? (1+5)	22	31.88	35	43.21	31	27.68	31	40.26	37	38.00	62	32.80
2. Do you usually cough first thing in the morning in summer? (2+5)	17	24.64	27	33.33	26	23.21	30	38 96	44	29.33	56	29.63
3 Do you usually cough during the day or night in winter? (1+3+5)	16	23 19	23	28.40	13	11.61	14	18 18	39	26.00	27	14.29
4 Do you usually cough during the day or night in summer? (2+4+5)	6	8.70	16	19.75	12	10.71	14	18.18	22	14.67	26	13.76
6. Do you usually bring up any phlegm from your chest first thing in the morning in winter? (6+10)	19	27.54	37	45.68	21	18.75	24	31 17	56	37.33	45	23.81
7 Do you usually bring up any phlegm from your chest first thing in the morning in summer? (7+10)	14	20.29	31	38.27	17	15 18	23	29.87	45	30.00	40	21 16
8. Do you bring up any phlegm from your chest during the day or night in winter? (6+8+10)	14	20.29	23	28 40	9	8.04	9	11.69	37	24.67	18	9.52
9 Do you bring up any phlegm from your chest during the day or night in summer? (7+9+10)	10	14 49	22	27 16	9	8.04	9	11.69	32	21.33	18	9.52

Table 21a (cont.)

Question	London				Bergen				London		Bergen	
Age	40-49		50-59		40-49		50-59		40-59		40-59	
	No. 69		No. 81		No. 112		No. 77		No. 150		No. 189	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
11a. Have you had this cough/phlegm less than 2 years?	3	4.35	5	6.17	0	–	2	2.60	8	5.33	2	1.06
11b. Have you had this cough/phlegm 2 years or more?	26	37.68	41	50 62	41	36.61	32	41.56	67	44.67	73	38.62
12b. In the past 3 years have you had a period of (increased) cough and phlegm lasting for 3 weeks or more? Only one period.	6	8.70	7	8.64	10	8.93	5	6.49	13	8.67	15	7.94
12c. In the past 3 years have you had period of (increased) cough and phlegm lasting for 3 weeks or more? 2 or more periods.	8	11.59	6	7 41	6	5.36	7	9.09	14	9.33	13	6.88
13b. Have you ever coughed up blood? Streaks.	1	1 45	3	3.70	1	0.89	2	2.60	4	2.67	3	1.59
13c. Have you ever coughed up blood? More.	4	5.80	2	2.47	0	–	1	1.30	6	4.00	1	0.53
14a. Are you ever troubled by shortness of breath when hurrying on the level or walking up a slight hill? (Dyspnoea gr II)	34	49.28	47	58.02	4	3.57	12	15.58	81	54.00	16	8.47
14b. Do you get short of breath when walking with other people at an ordinary pace on the level? (Dyspnoea gr III)	3	4.35	7	8.64	1	0.89	6	7.79	10	6.67	7	3.70
14c+d. Do you have to stop for breath when walking at your own pace on the level? Are you short of breath on washing or dressing? (Dyspnoea gr IV V.)	1	1.45	1	1.23	1	0.89	0	–	2	1.33	1	0.53
15a. Wheezing. Do you get this with colds?	13	21.74	11	13.58	26	23.21	23	29.87	26	17.33	49	25.93

Table 21a (cont.)

Table 21 a *contd*

Question	London				Bergen				London		Bergen	
	Age 40-49		50-59		40-49		50-59		40-59		40-59	
	No. 69		No. 81		No. 112		No. 77		No. 150		No. 189	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
15 b. Do you get this occasionally apart from colds?	10	14 49	12	14.81	16	14.29	11	14.29	22	14.67	27	14.29
15 c. Do you get this most days or nights?	9	13.04	21	25.93	7	6.25	7	9.09	30	20.00	14	7 41
17 Does the weather affect your chest?	19	27.54	27	33.33	23	20.54	22	28.57	46	30.67	45	23.81
21. During the past 3 years have you had any chest illness which has kept you off work, indoors, at home or in bed?	14	20.29	21	25.93	16	14.29	12	15.58	35	23.33	28	14.81
1 only	10	14 49	14	17.28	8	7 14	6	7.79	24	16.00	14	7 41
2 or more	4	5.80	7	8.64	8	7 14	6	7.79	11	7.33	14	7 41
Past illnesses												
22. Bronchitis	17	24.64	28	34.57	24	21 43	22	28.57	45	30.00	46	24.38
23 Pneumonia	12	17.39	16	19.75	24	21 43	22	28.57	28	18.67	46	24.38
24 Pleurisy	14	20.29	11	13.58	14	12.50	9	11.69	25	16.67	23	12.17
25 Pulmonary TBC	4	5.80	0	–	2	1.79	6	7.79	4	2.67	8	4.23
26. Bronchial asthma	2	2.90	1	1.23	–	–	1	1.30	3	2.00	1	0.53
Mean PRF litres/min.	439.6		384 9		513.7		452.0					

The numbers befor each question correspond to the number used in the MRC questionnaire.

Breathlessness A very marked difference is found between the two samples in the prevalence of dyspnoea gr II graded according to Fletcher (1952) At least part of this difference may be an artifact due to a different wording of this question in the two surveys. In the questionnaire used in Bergen, the following phrasing was used: Are you ever troubled by shortness of breath except on strenuous exertion?' and if the answer to this question was no it was checked by asking: 'Not even on hurrying on the level or walking up a slight hill?' In the questionnaire used in London, the following question was asked. Are you ever troubled by shortness of breath, when hurrying on the level or walking up a slight hill?

The prevalence of breathlessness gr II in this sample from London is however much higher than the rates found previously in samples of male workers in London by other investigators using the same questionnaire (Fletcher & Tinker 1960) To try to assess whether the high prevalence found might be due to the author's technique in interviewing the London sample, a comparison was made with another sample of mail van drivers interviewed at the same time by a British doctor using the same questionnaire. No difference in prevalence rates was found between these two series.

Wheezing There is little difference between the two samples in the proportion of men admitting to wheezing. A striking difference is found, however when the wheezing is graded according to severity More than half of the Norwegians who said that their chest had sounded wheezy had only experienced this with colds, and less than 10 per cent admitted to wheezing on most days or nights. In the London sample nearly 50 per cent of the men who had been wheezing, said that they had this symptom on most days or nights. The difference between the two samples is nearly the same in the lower and the higher of the age-groups given.

Other symptoms Proportionately more men in the British sample than in the Norwegian one said that they had coughed up blood. The numbers are, however small, and no inference can be made.

A slightly higher proportion of men in London said that the weather affected their chests. The difference between the groups is, however not statistically significant. Fog and damp weather were the predominant types said to have an adverse effect in both countries, and nearly all of the men affected said that these types of weather made them more breathless.

CHEST ILLNESSES WITHIN THE LAST 3 YEARS

From Table 21 a it will be seen that in both age-groups a higher proportion of men in the London sample than in the Norwegian one, have had chest illnesses within the last 3 years. The difference is not statistically significant at the 5 %

level. Splitting the groups into those who have had only one chest illness and those who have experienced 2 or more chest illnesses within this period, it is found that the observed difference is confined to the group with only one spell of disease. Recurrent chest illnesses thus seem to be as common in the Norwegian as in the British sample. In both countries the large majority of the recurrent illnesses are certified as bronchitis.

In this as well as in the following tables on sickness absence, the information obtained from the men during the interviews has been corrected from the data extracted from the men's sickness absence records. In London, 7 men who on questioning denied having had chest illnesses within the last 3 years, were found to have had sickness absence certified as bronchitis. Two men who said they had had chest illness within the period were not found in the absence records to have had certified absences. One of these men, however had only been employed in his present occupation for 15 months, and may have had a spell of chest illness previous to his present employment. In Bergen, 2 men who denied chest illnesses were found to have had certified absence ascribed to bronchitis within the 3 year period. Thus, in both samples it seems as if the information obtained on previous illnesses from the interviews tends to underestimate the sickness absence rates.

Table 21 b gives the total disease experience in the two populations during the 3 years preceding the surveys. It is found that in men over the age of 50, the rates for bronchitis are higher in the London group In all other disease groups the Bergen rates are higher in this age-group Under the age of 50 the picture is less clear but here also there seems to be a tendency to higher rates in the Bergen sample.

The difference between the samples in the rates for bronchitis in men over 50 years of age might be due to transfers from this diagnostic group to the groups Influenza and Other respiratory diseases' in the Bergen sample. If more serious respiratory diseases were included in these groups one would expect average duration per spell of illness to be longer From Table 21 b giving the average duration of certified sickness absence it will be seen that the duration per spell of Influenza and Other respiratory diseases is longer in the Bergen than in the London sample. This may suggest that these diagnostic groups in the Bergen sample include more severe cases of respiratory disease. The average duration of absence in the Bergen sample is also, however considerably longer for non respiratory diseases, suggesting that the length of sickness absence is determined to some extent by factors other than the seriousness of the certified cause of incapacity It therefore seems difficult to draw any conclusions regarding bronchitis morbidity from these data.

The comparability of disease experience within the last 3 years, is also restricted by the difference between the groups in duration of present employment. Thirty three men (22 %) in the London sample had been with the present

TABLE 21b

Morbidity 3 Years Preceding Surveys

Spells of illness per 1,000 man years

Age at time of survey	Bronchitis		Pneumonia		Influenza		Other resp. diseases		All other diseases		Total	
	L	B	L	B	L	B	L	B	L	B	L	B
40-	68.4	84.4	10.8	13.3	204.0	253.3	295.2	337.8	862.8	640.0	1441.2	1328.9
45-	54.0	45.0	0.0	27.0	294.0	180.2	108.0	117.1	573.6	630.6	1029.6	1000.0
50-	76.8	47.6	0.0	0.0	160.8	333.3	164.8	156.9	372.0	581.1	776.4	1118.9
55-59	219.6	135.0	0.0	15.5	170.4	263.6	150.0	178.3	460.8	620.2	1000.8	1232.6

Morbidity 3 Years Preceding Surveys

Duration of absence per spell of illness

Age at time of survey	Bronchitis		Pneumonia		Influenza		Other resp. diseases		All other diseases		Total	
	L	B	L	B	L	B	L	B	L	B	L	B
40-	11.0	13.6	13.0	28.7	6.1	10.1	24.0	11.1	9.3	27.3	11.9	18.6
45-	17.4	21.2	–	28.3	8.9	11.9	16.9	13.3	15.3	26.9	13.8	22.4
50-	14.0	16.4	–	–	7.4	11.3	7.1	10.8	13.7	33.9	11.1	23.2
55-59	20.1	18.2	–	11.5	10.5	10.9	12.8	14.0	11.7	35.2	13.5	23.1

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The comparability of disease experience within the last 3 years, is also restricted by the difference between the groups in duration of present employment. Thirty three men (22 %) in the London sample had been with the present

the other hand, pneumonia is reported more often by the Bergen men. This disparity may be due to differences in diagnostic habits and medical terminology and if bronchitis and pneumonia are grouped together the prevalence rates in the two samples are almost identical in each of the 10-year age-groups.

In summary respiratory symptoms were rather prevalent in both of the samples. The main differences between the countries are found in the more serious symptoms, i.e. cough all day in the winter production of phlegm, breathlessness and chest illnesses within the last 3 years. Some of the respiratory symptoms will, in later sections of the paper be related to various other factors studied.

SMOKING HABITS

In Table 22, Fig. 26, the men in the two samples are classified according to their present smoking habits. The classification is the one used in most studies that have been carried out by British workers and which has been proposed as a standard classification by The Medical Research Council's Committee on the Aetiology of Chronic Bronchitis (1960) It is found that the proportions of non-smokers and ex-smokers are practically the same in the two populations. Among present smokers there are, however striking differences in the amount of tobacco smoked. The majority of the Norwegian smokers are found in the lowest consumption category and less than 2 per cent are smoking more than 25 grams a day In the British sample 50 per cent are smoking 15 grams/day or more, and 11 per cent exceed a consumption of 25 grams/day There is no age trend in the levels of consumption in any of the two samples. From Table 23 Fig. 27 giving the distribution of present smokers by product smoked, it will be seen that the British not only dif

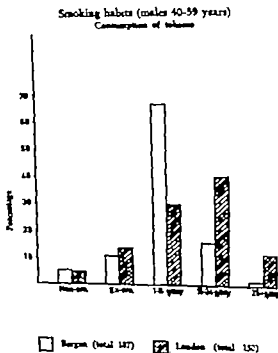


Fig. 26

employer for less than 3 years, and no sickness absence records were available for that part of the 3 year period in which they were in other jobs. In the Bergen sample all the men had more than 3 years employment in present jobs, and sickness absence records were consequently available for the whole period. As the interview data tend to give lower morbidity rates than those obtained from sickness absence records, this disparity between the two samples will probably tend to reduce the rates found in the British sample compared with those observed in the Norwegian one.

PAST CHEST ILLNESSES

The differences found in past chest illness experience between the two samples are remarkably small considering the disparities between the two countries suggested by the available statistical data on morbidity and mortality. The prevalence of bronchitis and of pleurisy is a little higher in the London sample on

TABLE 22

Present Smoking Habits

Levels of consumption

Age	40-				45-				50-			
	London		Bergen		London		Bergen		London		Bergen	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Non smokers	2	7.41	5	6.57	4	9.52	4	10.81	1	2.04	–	–
Ex smokers	3	11.11	5	6.67	6	14.29	6	16.22	4	8.16	4	11.76
1-14 g/day	8	29.63	51	68.00	15	35.11	21	56.76	15	30.61	24	70.59
15-24 g/day	12	44.44	13	17.33	15	35.71	4	10.81	20	40.82	6	17.65
25+ g/day	2	7.41	1	1.33	2	4.76	2	5.41	9	18.37	–	–
Total	27	100.00	75	100.00	42	99.99	37	100.01	49	100.00	34	100.00

	55-				40-59			
	London		Bergen		London		Bergen	
	No.	%	No.	%	No.	%	No.	%
Non-smokers	–	–	1	2.33	7	4.67	10	5.29
Ex-smokers	8	25.00	5	11.63	21	14.00	20	10.58
1-14 g/day	8	25.00	30	69.77	46	30.67	126	66.67
15-24 g/day	12	37.50	7	16.28	59	39.33	30	15.87
25+ g/day	4	12.50	–	–	17	11.33	3	1.59
Total	32	100.00	43	100.00	150	100.00	189	100.00

the other hand, pneumonia is reported more often by the Bergen men. This disparity may be due to differences in diagnostic habits and medical terminology and if bronchitis and pneumonia are grouped together the prevalence rates in the two samples are almost identical in each of the 10-year age-groups.

In summary respiratory symptoms were rather prevalent in both of the samples. The main differences between the countries are found in the more serious symptoms, i.e. cough all day in the winter production of phlegm, breathlessness and chest illnesses within the last 3 years. Some of the respiratory symptoms will, in later sections of the paper be related to various other factors studied.

SMOKING HABITS

In Table 22, Fig. 26, the men in the two samples are classified according to their present smoking habits. The classification is the one used in most studies that have been carried out by British workers and which has been proposed as a standard classification by The Medical Research Council's Committee on the Aetiology of Chronic Bronchitis (1960) It is found that the proportions of non-smokers and ex-smokers are practically the same in the two populations. Among present smokers there are, however striking differences in the amount of tobacco smoked. The majority of the Norwegian smokers are found in the lowest consumption category and less than 2 per cent are smoking more than 25 grams a day In the British sample 50 per cent are smoking 15 grams/day or more, and 11 per cent exceed a consumption of 25 grams/day There is no age trend in the levels of consumption in any of the two samples. From Table 23 Fig. 27 giving the distribution of present smokers by product smoked, it will be seen that the British not only dif

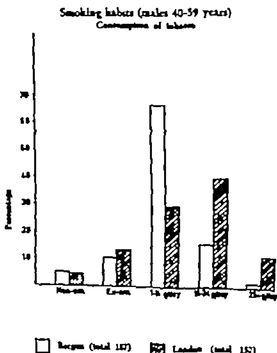


Fig. 26

fer from the Norwegians concerning the amount of tobacco smoked, but there is in the London sample a higher proportion of pure cigarette-smokers than in the Bergen sample, and conversely the proportion of mixed smokers is higher in Norway. The proportion of pipe- and/or cigar smokers is the same in the two samples. These differences are statistically highly significant ($P < 0.0005$)

In the Norwegian sample a slight decrease by age is found in the proportion of pure cigarette-smokers. This trend is not *seen in* the British sample, but the numbers in each age-group are small in both samples. It is conceivable, however that this may reflect the time trend observed *in* the national cigarette consumption, which suggests that cigarette-smoking became a common habit among Norwegian males later than among their British counterparts. About 90 % of the Norwegian cigarette-smokers were rolling their own cigarettes, whereas in the London sample only 50 % of the cigarette-smokers had the same habit. The rest of them smoked manufactured cigarettes of various brands.

SPUTUM PRODUCTION

Table 24 gives the distribution of morning sputum volumes. The differences between the samples are small, but the relatively high proportion of sputum bottles not returned in the British sample necessitates caution in making com-

TABLE 23

Present Smokers by Product Smoked

Male 40-59 years

Age	40-				45-				50-			
	London		Bergen		London		Bergen		London		Bergen	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Cigarettes	19	86.4	52	80.0	29	90.6	22	81.5	41	93.2	19	63.3
Pipe/cigars	3	13.6	–		–		–		3	6.8	5	16.7
Mixed	–		13	20.0	3	9.4	5	18.5	–		6	20.0
Total	22	100.0	65	100.0	32	100.0	27	100.0	44	100.0	30	100.0

Age:	55-				40-59			
	London		London		Bergen		Bergen	
	No.	%	No.	%	No.	%	No.	%
Cigarettes	24	100.0	28	75.7	113	92.6	121	76.1
Pipe/cigars	–		3	8.1	6	4.9	8	5.0
Mixed	–		6	16.2	3	2.5	30	18.9
Total	24	100.0	37	100.0	122	100.0	159	100.0

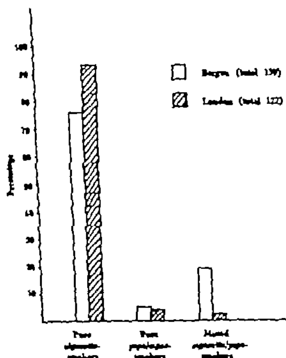


Fig. 27

parisons. From the cross-tabulation of answers to questions on phlegm and of returned sputum volumes (Table 25), it is found that more than $^3/_4$ of the men not returning their bottles denied morning phlegm production. It thus seems unlikely that the category not returned should invalidate the comparison to any great extent.

In order to find if any relation existed between the answers to the symptom questionnaire and the phlegm production, these data were cross-tabulated. Table 25 gives the results for the London and the Bergen sample separately. Considering that the questions refer to usual habit (production of phlegm lasting 3 months or more), it is not surprising that 33 % of the men who denied usual production of phlegm returned sputum specimens. The subjects usually free from phlegm may have a short period of expectoration, and conversely the persons answering that they usually produce phlegm may fail to do so on the particular day the specimens are collected. The percentage agreement in the two samples is nearly identical, and is of the same order as that found by Fletcher et al (1959) in their study of London postmen.

All sputum specimens were inspected by the author who classified them according to their appearance. The results are given in Table 26. No differences are found in the distribution of the appearance of sputum. In both samples it is found that the volume increases as the sputum becomes more abnormal.

VENTILATORY CAPACITY

As will be seen from Table 21 a, the mean peak respiratory flow (PRF) was lower in the British sample in both the age-groups given in the table, compared

with the Norwegian sample. A definite decrease with age is found in both samples. In order to see if this difference was caused by the higher proportion of subjects with various respiratory symptoms in the British sample, the populations have been divided in groups of normals and symptoms. The symptom groups consist of the persons giving a positive answer to the questions on cough and/or phlegm lasting for 3 months or more, and/or admitting having breathlessness gr. II or more. This grouping is the same as the one used by

TABLE 24

Distribution of Sputum Volumes

Place	London				Bergen			
Age	40–49		50–59		40–49		50–59	
	No.	%	No.	%	No.	%	No.	%
Nil	32	46.4	22	27.2	69	61.6	33	42.9
0-	8	11.6	8	9.9	13	11.6	8	10.4
2	12	17.4	27	33.3	14	12.5	17	22.1
6+	3	4.4	13	16.1	12	10.7	15	19.5
Not ret.	14	20.3	11	13.6	4	3.6	4	5.2
Total	69	100.1	81	100.1	112	100.0	77	100.1

TABLE 25

Relationship between Answers to Questions and Sputum Volumes

London

Sputum volume:	Nil	0-	2	6+	N.R.
Answers to quest.					
No phlegm	50	11	12	2	19
Phlegm on rising	2	2	10	3	2
Phlegm all day	2	3	17	11	4
Total	54	16	39	16	25

Bergen

Sputum volume:	Nil	0-	2	6+	N.R.
Answers to quest.					
No phlegm	100	18	17	5	4
Phlegm on rising	2	1	10	11	3
Phlegm all day	0	2	4	11	1
Total	102	21	31	27	8

TABLE 26

Relationship between Sputum Volumes and Appearance of Sputum

London

Ages	40-49			50-59			40-59		
Volume	0-	2	6+	0-	2	6+	0-	2	6+
Saliva	3	—	—	3	1	—	6	1	—
Mucoid	4	4	3	5	13	7	9	17	10
Muco-purulent	1	8	—	—	10	6	1	18	6
Purulent	—	—	—	—	3	—	—	3	—
Total	8	12	3	8	27	13	16	39	16

Bergen

Ages	40-49			50-59			40-59		
Volumes	0-	2	6+	0-	2	6+	0-	2	6+
Saliva	3	—	—	—	2	—	3	2	—
Mucoid	8	10	3	8	13	8	16	23	11
Muco-purulent	2	4	9	—	2	7	2	6	16
Total	13	14	12	8	17	15	21	31	27

Fletcher *et al.* (1959). The small numbers obtained in the subgroups necessitated the comparison to be made in the total samples and not in separate age-groups.

In order to eliminate any effect of differences between the samples in the distribution of age and sitting height (stem height), a multiple regression analysis of peak respiratory flow on these two variables was carried out, using the subjects in the two normal populations. Neither in each separate sample nor in the pooled sample was the sitting height found to be significantly related to PRF when allowance was made for age. Excluding sitting height from the analysis the regression of PRF on age was calculated for the sample from each country separately. In the British sample a fall of 4.3 litres/min. per year was found, in the Norwegian sample the figure was 4.1 litres/min. per year. In the pooled population there was a fall of 4.2 litres/min. per year and this value has been used to standardize PRF to age 40 in both samples.

Table 27, Fig. 28 shows the distribution of the age-standardized PRF for the normal' and the symptom groups in London and Bergen. In both samples a greater variation *is found in the PRF* among the men with symptoms than among the men without cough, phlegm or breathlessness, and as would be expected, the mean is higher in the group of normals *than in the symptom* group. Comparing the two countries we find that among the normals' as well as among the subjects with symptoms, higher PRF values are found in the Norwegian than

in the British sample. The variance of the PRF distribution in normals is similar in the London and in the Bergen samples, but larger in the former than in the latter sample in the symptom group

OTHER FACTORS

The blood pressure measurements were carried out in order to see if there was any difference in the proportion of men with hypertension in the two samples, as hypertensive manifestations may possibly influence the prevalence of respiratory symptoms To include such measurements in surveys of chronic cardio-respiratory diseases, was recommended by the study group convened by The Council for International Organizations of Medical Sciences (1959) In Table 19 is given the number of men in each sample with systolic blood pressure above 160 mm Hg and/or diastolic pressure above 95 mm Hg. No significant difference is found between the samples in the proportion of men with blood pressure exceeding these arbitrary limits.

In the Norwegian sample 26 men (14 %) had abnormal mass chest X ray pictures within the last 2 years. The term abnormal is here used to describe all

TABLE 27

Distribution of Peak Respiratory Flow

(Standardized to age 40)

	Symptoms		Normals		Total	
	London	Bergen	London	Bergen	London	Bergen
PRF						
200 litres/min.	3	1	–	–	3	1
200-	4	2	–	–	4	2
250-	10	2	2	–	12	2
300-	9	6	3	4	12	10
350-	11	9	5	6	16	15
400-	16	9	6	9	22	18
450-	22	11	10	18	32	29
500-	10	13	2	17	12	30
550-	16	7	5	27	21	34
600-	6	8	3	17	9	25
650-	2	1	2	9	4	10
700-	1	2	–	9	1	11
750+	2	–	–	2	2	2
Total	112	71	38	118	150	189
Mean PRF	445.6	471.9	468.3	550.7	451.3	521 1
S. D	129 0	117.0	103.0	105.0		

X-ray pictures in which the examining radiologist recorded any abnormality. Most of these were minor abnormalities and old lesions probably without any significance for the prevalence of respiratory symptoms and the results of lung function test. No corresponding figures are available for the British sample, as mass X ray examination is not compulsory for the Post Office employees.

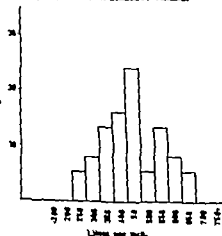


Fig. 28

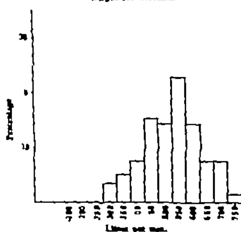


Fig. 28 b

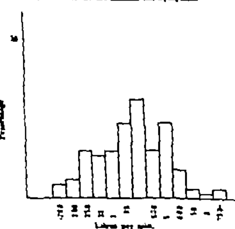


Fig. 28 c

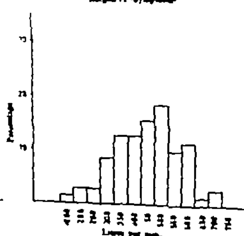


Fig. 28 d

In the British sample electrocardiograms (11 leads) were recorded on all the men. The results are summarized in Table 19 Twenty-eight men (19 %) were found to have some abnormalities in their resting ECG No corresponding data are available for the Norwegian sample. The importance of abnormal ECG in relation to the symptoms under study is not known, but it seems unlikely that possible differences between the samples in this factor would invalidate the comparison of respiratory symptomatology

Comparison with other surveys

The comparability of the prevalence of respiratory symptoms and ventilatory capacity found in surveys carried out by different workers, is restricted. There is a considerable variation between observers using standardized questionnaires, and Fairbairn *et al* (1960) found that peak respiratory flow recordings are also liable to observer variation. The reading depends on the force put into the effect of blowing (McDermott & McKerrow 1956) and differences in the in-

TABLE 28

Percentage of Respiratory Symptoms in Various Populations Surveyed

	Annandale	Bône	London Postmen	London P O Drivers	Bergen
	(Higgins *et al.*)	(Olsen *et al.*)	(Fletcher *et al.*)	(Mork)	(Mork)
	55-64 years	55-64 years	50-59 years	50-59 years	50-59 years
	No. 87	No. 156	No. 96	No. 81	No. 77
Cough on rising winter		16	54	43	40
– on rising summer		2	39	33	39
– all day winter	29 (Cough)	1	20	28	18
– all day summer		0	12	20	18
Phlegm on rising winter		10	47	46	31
– on rising summer		1	3	38	30
– all day winter	23 (Phlegm)	1	25	28	12
– all day summer		0	13.3	27	12
Haemoptysis	6	0		6	7
Dyspnoea gr II		11	20	59	16
– gr III		15	14	9	8
– IV+V		0.5	2	1	0
Wheeze occasionally	44 (Wheeze)	16	50	28	44
– most days		0.5	20	26	9
Chest affected by weather	10.3	10	41	33	29
– *Illnesses last 3 years:*					
1 only	14	6	15	17	8
2+	5	0	25	9	8
PRF	441	470		385	452

struction given and the co-operation achieved when doing the test will influence the results.

The data given in Table 28 summarize the results from a number of studies carried out in different communities by various workers. The symptomatic questionnaires used are almost identical with respect to the symptoms in the table, but even so caution is needed in making inferences from these data.

It will be seen that the London group in the present study is very similar in most symptoms to the sample of Post Office workers in London surveyed by Fletcher *et al.* (1959) The large difference in the prevalence of dyspnoea gr II has been commented upon in earlier sections of this paper The rates given for recurrent chest illnesses are also higher in Fletcher's sample than in the present study population, but this is due to the inclusion in the former sample of spells of illness, certified as influenza lasting more than 6 days. If such cases are included in the present London sample, the percentage of men with one chest illness only increases to 25 and 26 % of the men are found to have recurrent chest illnesses. This is the same proportion of recurrent chest illnesses as found by Fletcher *et al.* (1959) In both studies the data on chest illnesses were extracted from the men's sickness absence records.

Higgins & Cochran (1958) have published the results of a survey in an agricultural population in Annandale, Scotland. Their publication, unfortunately does not give sufficiently detailed results to make comparison between each separate symptom possible. From the data given, it seems as if the prevalence of respiratory symptoms in this agricultural community is rather similar to the rates found in Bergen, and the mean PRF is also nearly the same. The Annandale population is, however on an average 5 years older than the Bergen population. Compared with the results from Rönne, Bornholm, published by Olsen & Gilson (1960) the rates in Bergen are found consistently higher and the mean PRF is higher in Rönne, although the Danish men are on an average 5 years older The exposure to air pollution in these two samples is probably rather similar but the groups differ significantly in their smoking habits with a higher proportion of cigarette-smokers in the Bergen sample.

Discussion

The comparability of prevalence rates based on symptomatic questionnaires is influenced by a number of factors. The most important is probably the variation between observers, which may be considerable even when trained interviewers are using the same standardized questionnaire (Fairbairn *et al.* 1959) This variability is eliminated in this study as all interviews were carried out by the same investigator The variability that might have been introduced by the increase in the investigator's experience during the survey period, is probably small. Another

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	55-64 years	55-64 years	50-59 years	50-59 years	50-59 years
	No. 87	No. 156	No. 96	No. 81	No. 77
h on rising winter		16	54	43	40
on rising summer		2	39	33	39
all day winter	29 (Cough)	1	20	28	18
all day summer		0	12	20	18
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all day winter	23 (Phlegm)	1	25	28	12
all day summer		0	13.5	27	12
optysis	6	0		6	7
noea gr II		11	20	59	16
gr III		15	14	9	8
IV+V		0.5	2	1	0
ze occasionally	44 (Wheeze)	16	50	28	44
most days		0.5	20	26	9
affected by weather	10.3	10	41	33	29
illnesses last 3 years:					
1 only	14	6	15	17	8
2+	5	0	25	9	8
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rising winter		16	54	43	40
rising summer		2	39	33	39
lay winter	29 (Cough)	1	20	28	18
day summer		0	12	20	18
rising winter		10	47	46	31
rising summer		1	32	38	30
lay winter	23 (Phlegm)	1	25	28	12
lay summer		0	13.5	27	12
sis	6	0		6	7
gr II		11	20	59	16
III		15	14	9	8
-V		0.5	2	1	0
ccasionally	44 (Wheeze)	16	50	28	44
days		0.5	20	26	9
cted by weather	10.3	10	41	33	29
sses last 3 years		6	15	17	8
dy	14	0	25	9	8
	5			385	452
	441	470			

between the two total populations. It seems likely however that this difference in retirement rates between the samples may to some extent cause an underestimation of the disparity in past chest illness experience when occupational groups are compared.

The differences found between the populations in anthropometric measurements and occupational and socio-economic factors can hardly account for the differences found in the prevalence of respiratory symptoms and lung function. The two groups show however a considerable disparity in their exposure to two of the factors that have been suggested as of importance in the causation of chronic cardio-respiratory diseases, i.e. cigarette-smoke and atmospheric pollution.

It has been found that there is a quantitative as well as a qualitative difference in smoking habits between the two populations. The British men have a higher tobacco consumption, and pure cigarette-smokers are significantly more common than among the Norwegian men.

Smoking histories are liable to be affected by a number of uncertainties. Todd & Laws (1958) in their study of the reliability of statements about smoking habits, found that reluctance to admit the real amount smoked probably leads to an underestimate of the real consumption. There is no reason to believe that this factor differs quantitatively to any great extent in the two samples in the present investigation. In relation to chronic diseases it may be more important that no comparable information has been collected on past smoking habits. Such information is, however usually rather inaccurate, and Todd & Laws (1958) in this context quote Sir Frederic Bartlett's (1950) maxim that accurate recall is the exception and not the rule In the Bergen sample changes within the last 10 years were asked for and a surprisingly high proportion (91 %) of the men maintained that they had not changed their tobacco consumption during

TABLE 29

Ill-health Retirements and Deaths 3 Years Preceding Surveys

Age at time of retirement or death	London		Bergen	
	Retirements	Deaths	Retirements	Deaths
	No.	No.	No.	No.
40-	4	–	–	1
45-	1	–	–	2
50-	2	2	–	2
55-	2	2	–	1
40-59	9	4	0	6

factor that may influence the comparability in this type of investigation, is possible differences between the populations in the emphasis laid on different symptoms. In a community where certain minor' symptoms — as for instance cough — are common in the general population, a slight cough may be regarded as more or less normal. This view may influence the memory of the occurrence of such symptoms, and they may not be mentioned in the interviews. On the other hand, symptoms may be more often recalled and mentioned in samples from populations where their prevalence is generally low This may tend to diminish differences that may exist between groups from different communities.

The comparative study of respiratory symptoms in the samples from Bergen and *London* has demonstrated a lower prevalence of some of the more serious respiratory symptoms in the Norwegian group In past chest illness experience the difference between the groups is small. This is in contrast to the picture derived from the analysis of national figures on morbidity and mortality Considering that the comparisons are carried out between two occupational groups, it is obvious that the prevalence rates found in the two samples may give a distorted picture, if the selection into the particular occupation, as well as the selection out of the service, is not similar in the two populations. The question of differences in the selection into the occupation in the two countries has been discussed in a previous section of the paper and found to be probably without decisive importance for the prevalence rates observed.

Table 29 gives the deaths and retirements due to ill-health in the two populations in the 3 years preceding the field surveys. It is found that whereas the mortality rates are of the same order the retirement rates are quite different in the two samples. In Bergen there were no retirements during the period compared with 9 in the London sample. The retirement rate in the London sample is 2.42 % of present staff in the 40-49-year age-group and 1 65 % in the 50-59 year age-group. The total wastage rate (retirements and deaths) in the 50-59-year age-group is 3.29 %. These rates do not differ much from the rates for retirements and deaths observed by Roberts & Reid (1954) in their analysis of premature disablement and death among Post Office workers in England & Wales. The causes of death are not known in the British sample. In the Norwegian sample one death in the 50-59-year age-group was certified as bronchitis, the rest of the deaths were caused by cancer or arteriosclerotic heart disease. None of these persons had had any spells of chest illness during the period they were exposed to risk within the last 3 years. Among the 9 men retired in the London sample 6 spells of bronchitis were recorded, or 631 6 spells per 1 000 men/year exposure to risk. This figure is much higher than the rates given in Table 21 b suggesting that the men forced to retire differ from the remaining population in their chest illness experience. As data on retirements and disease among the men retired are only available for a 3 year period, it is impossible to assess quantitatively the effect this factor may have on the comparability

this period. This in accordance with Todd & Lawe's (1958) finding that continuity of habit is, over shorter periods, the most common experience. This feature will tend to diminish the errors involved in the assumption that current smoking habits are a guide to past levels of tobacco consumption, and therefore relevant to the present prevalence of chronic diseases.

In order to try to assess the effect of smoking independently of a coinciding effect of atmospheric pollution, the prevalence of respiratory symptoms has been calculated for each consumption category in each sample. The results are given in Table 30. It is found that in both samples there is an increase in the prevalence of cough and phlegm with increasing tobacco consumption. This finding is in accordance with those of Higgins (1957), Fletcher *et al.* (1959) and Higgins *et al.* (1959). The rates for other respiratory symptoms and for chest illnesses in the last 3 years, do not show any definite trend in relation to tobacco consumption in any of the samples.

When comparing the two samples it emerges that apart from in the 40–49 age-group in the lowest consumption category the prevalence of cough and phlegm in the Bergen sample is as high as or higher than in the corresponding age- and consumption groups in the London sample. The numbers in some of the subgroups are admittedly small, but there is a definite consistency in the various symptoms. This similarity between the two samples in the prevalence of these symptoms in corresponding consumption categories, suggests that the prevalence of cough and phlegm is mainly determined by the amount smoked, irrespective of other environmental factors such as exposure to atmospheric pollution. The findings in the present study correspond to Higgins's (1957) observation of similarity in the prevalence of cough and phlegm in an agricultural population in the Vale of Glamorgan and in an industrial population in Leigh. The comparability between the populations of breathlessness gr. II seems, as pointed out previously dubious, and for gr. III and more the numbers in the different subgroups are too small to allow any inferences to be made. The rates for chest illnesses in the last 3 years tend to be higher in the British sample compared with Norwegian men in corresponding smoking categories.

Table 31 gives the Peak Respiratory Flow (standardized to age 40) in the two samples by levels of consumption. In all smoking categories the mean PRF is higher in the Bergen than in the London sample. In the Norwegian sample there is a significant fall in PRF with increasing consumption of tobacco. In the British sample the differences between mean PRF in various consumption categories are small. That no difference is found between non-smokers and smokers in the British sample may be due to the small number of non-smokers, and no inferences can be made from this finding. The observed significant difference between smokers and non-smokers in the Norwegian sample is in accordance with the findings of Fletcher *et al.* (1959) in a sample of Post Office workers in London, and similar observations were made by Higgins (1959) in samples

TABLE 30

Prevalence of Respiratory Symptoms in Different Smoking Groups

	1-14 g/day								15-24 g/day								25+ g/day							
Age:	40-		40-		50-		50-		40-		40-		50-		50-		40-		40-		50-		50-	
	London		Bergen		London		Bergen		London		Bergen		London		Bergen		London		Bergen		London		Bergen	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1)	9	39.1	19	26.4	5	21.7	18	33.4	10	37.0	10	58.8	17	53.1	11	84.6	2		1		11	84.6		
2)	8	34.8	16	22.2	3	13.0	17	31.5	8	29.6	9	52.9	13	40.6	11	84.6	—		1		9	69.2		
3)	8	34.8	9	12.5	1	4.4	6	11.1	6	22.2	4	23.5	12	37.5	7	53.9	2		—		8	61.5	—	
4)	3	13.0	8	11.1	1	4.4	6	11.1	3	11.1	4	23.5	9	28.1	7	53.9	—		—		4	30.8	—	
6)	9	39.1	12	16.7	7	30.4	15	27.8	7	25.9	8	47.1	17	53.1	7	53.9	2		—		10	76.9	—	
7)	7	30.4	9	12.5	6	26.1	14	25.9	5	18.5	8	47.1	11	34.4	7	53.9	1		—		11	84.6	—	
8)	7	30.4	6	8.3	3	13.0	5	9.3	6	22.2	3	17.7	11	34.4	3	23.1	1		—		6	46.2	—	
9)	5	21.7	6	8.3	5	21.7	5	9.3	4	14.8	3	17.7	6	18.8	3	23.1	1		—		8	61.5	—	
14a)	13	56.5	3	4.2	12	52.2	11	20.4	17	63.0	1	5.9	18	56.3	1	7.7	1		—		8	61.5	—	
14b)	2	8.7	1	1.4	2	8.7	1	1.9	1	3.7	—		2	6.3	4	30.8	—		—		2	15.4	—	
14c+d)	1	4.4	1	1.4	—	—	—		—		—		1	3.1			—		—		—		—	
17)	8	34.8	16	22.2	9	39.1	13	24.1	6	22.2	3	17.7	11	34.4	7	53.9	1		—		3	23.1	—	
21)	6	26.1	9	12.5	6	26.1	10	18.5	4	14.8	4	23.5	9	28.1	1	7.7	2		—		4	30.8	—	

The numbers in the left column correspond to the question numbers in the MRC questionnaire.

this period. This in accordance with Todd & Laws's (1958) finding that continuity of habit is, over shorter periods, the most common experience. This feature will tend to diminish the errors involved in the assumption that current smoking habits are a guide to past levels of tobacco consumption, and therefore relevant to the present prevalence of chronic diseases.

In order to try to assess the effect of smoking independently of a coinciding effect of atmospheric pollution, the prevalence of respiratory symptoms has been calculated for each consumption category in each sample. The results are given in Table 30. It is found that in both samples there is an increase in the prevalence of cough and phlegm with increasing tobacco consumption. This finding is in accordance with those of Higgins (1957), Fletcher *et al.* (1959) and Higgins *et al* (1959). The rates for other respiratory symptoms and for chest illnesses in the last 3 years, do not show any definite trend in relation to tobacco consumption in any of the samples.

When comparing the two samples it emerges that apart from in the 40-49 age-group in the lowest consumption category the prevalence of cough and phlegm in the Bergen sample is as high as or higher than in the corresponding age- and consumption groups in the London sample. The numbers in some of the subgroups are admittedly small, but there is a definite consistency in the various symptoms. This similarity between the two samples in the prevalence of these symptoms in corresponding consumption categories, suggests that the prevalence of cough and phlegm is mainly determined by the amount smoked, irrespective of other environmental factors such as exposure to atmospheric pollution. The findings in the present study correspond to Higgins's (1957) observation of similarity in the prevalence of cough and phlegm in an agricultural population in the Vale of Glamorgan and in an industrial population in Leigh. The comparability between the populations of breathlessness gr. II, seems, as pointed out previously dubious, and for gr. III and more the numbers in the different subgroups are too small to allow any inferences to be made. The rates for chest illnesses in the last 3 years tend to be higher in the British sample compared with Norwegian men in corresponding smoking categories.

Table 31 gives the Peak Respiratory Flow (standardized to age 40) in the two samples by levels of consumption. In all smoking categories the mean PRF is higher in the Bergen than in the London sample. In the Norwegian sample there is a significant fall in PRF with increasing consumption of tobacco. In the British sample the differences between mean PRF in various consumption categories are small. That no difference is found between non-smokers and smokers in the British sample may be due to the small number of non-smokers, and no inferences can be made from this finding. The observed significant difference between smokers and non smokers in the Norwegian sample is in accordance with the findings of Fletcher *et al.* (1959) in a sample of Post Office workers in London, and similar observations were made by Higgins (1959) in samples

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TABLE 30

Prevalence of Respiratory Symptoms in Different Smoking Groups

	1-14 g/day								15-24 g/day								25+g/day							
Age	40-		40-		50-		50-		40-		40-		50-		50-		40-		40-		50-		50-	
	London		Bergen		London		Bergen		London		Bergen		London		Bergen		London		Bergen		London		Bergen	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1)	9	39.1	19	26.4	5	21.7	18	33.4	10	37.0	10	58.8	17	53.1	11	84.6	2		1		11	84.6		
2)	8	34.8	16	22.2	3	13.0	17	31.5	8	29.6	9	52.9	13	40.6	11	84.6	—		1		9	69.2		
3)	8	34.8	9	12.5	1	4.4	6	11.1	6	22.2	4	23.5	12	37.5	7	53.9	2		—		8	61.5	—	
4)	3	13.0	8	11.1	1	4.4	6	11.1	3	11.1	4	23.5	9	28.1	7	53.9	—		—		4	30.8	—	
6)	9	39.1	12	16.7	7	30.4	15	27.8	7	25.9	8	47.1	17	53.1	7	53.9	2		—		10	76.9	—	
7)	7	30.4	9	12.5	6	26.1	14	25.9	5	18.5	8	47.1	11	34.4	7	53.9	1		—		11	84.6	—	
8)	7	30.4	6	8.3	3	13.0	5	9.3	6	22.2	3	17.7	11	34.4	3	23.1	1		—		6	46.2	—	
9)	5	21.7	6	8.3	5	21.7	5	9.3	4	14.8	3	17.7	6	18.8	3	23.1	1		—		8	61.5	—	
14a)	13	56.5	3	4.2	12	52.2	11	20.4	17	63.0	1	5.9	18	56.3	1	7.7	1		—		8	61.5	—	
14b)	2	8.7	1	1.4	2	8.7	1	1.9	1	3.7	—		2	6.3	4	30.8	—		—		2	15.4	—	
14c+d)	1	4.4	1	1.4	—	—	—		—		—		1	3.1			—		—		—		—	
17)	8	34.8	16	22.2	9	39.1	13	24.1	6	22.2	3	17.7	11	34.4	7	53.9	1		—		3	23.1	—	
21)	6	26.1	9	12.5	6	26.1	10	18.5	4	14.8	4	23.5	9	28.1	1	7.7	2		—		4	30.8	—	

The umbers in the left column correspond to the question numbers in the MRC questionnaire.

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TABLE 30

Prevalence of Respiratory Symptoms in Different Smoking Groups

	1-14 g/day								15-24 g/day								25+g/day							
Age	40-		40-		50-		50-		40-		40-		50-		50-		40-		40-		50-		50-	
	London		Bergen		London		Bergen		London		Bergen		London		Bergen		London		Bergen		London		Bergen	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1)	9	39.1	19	26.4	5	21.7	18	33.4	10	37.0	10	58.8	17	53.1	11	84.6	2		1		11	84.6		
2)	8	34.8	16	22.2	3	13.0	17	31.5	8	29.6	9	52.9	13	40.6	11	84.6	—		1		9	69.2		
3)	8	34.8	9	12.5	1	4.4	6	11.1	6	22.2	4	23.5	12	37.5	7	53.9	2		—		8	61.5	—	
4)	3	13.0	8	11.1	1	4.4	6	11.1	3	11.1	4	23.5	9	28.1	7	53.9	—		—		4	30.8	—	
6)	9	39.1	12	16.7	7	30.4	15	27.8	7	25.9	8	47.1	17	53.1	7	53.9	2		—		10	76.9	—	
7)	7	30.4	9	12.5	6	26.1	14	25.9	5	18.5	8	47.1	11	34.4	7	53.9	1		—		11	84.6	—	
8)	7	30.4	6	8.3	3	13.0	5	9.3	6	22.2	3	17.7	11	34.4	3	23.1	1		—		6	46.2	—	
9)	5	21.7	6	8.3	5	21.7	5	9.3	4	14.8	3	17.7	6	18.8	3	23.1	1		—		8	61.5	—	
14a)	13	56.5	3	4.2	12	52.2	11	20.4	17	63.0	1	5.9	18	56.3	1	7.7	1		—		8	61.5	—	
14b)	2	8.7	1	1.4	2	8.7	1	1.9	1	3.7	—		2	6.3	4	30.8	—		—		2	15.4	—	
14c+d)	1	4.4	1	1.4	—	—	—		—		—		1	3.1			—		—		—		—	
17)	8	34.8	16	22.2	9	39.1	13	24.1	6	22.2	3	17.7	11	34.4	7	53.9	1		—		3	23.1	—	
1)	6	26.1	9	12.5	6	26.1	10	18.5	4	14.8	4	23.5	9	28.1	1	7.7	2		—		4	30.8	—	

The numbers in the left column correspond to the question numbers in the MRC questionnaire.

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TABLE 30

Prevalence of Respiratory Symptoms in Different Smoking Groups

	1 14 g/day								15-24 g/day								25+g/day							
Age	40-		40-		50-		50-		40-		40-		50-		50-		40-		40-		50-		50-	
	London		Bergen		London		Bergen		London		Bergen		London		Bergen		London		Bergen		London		Bergen	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1)	9	39 1	19	26.4	5	21.7	18	33 4	10	37.0	10	58.8	17	53 1	11	84.6	2		1		11	84.6		
2)	8	34.8	16	22.2	3	13.0	17	31.5	8	29.6	9	52.9	13	40.6	11	84.6	—		1		9	69.2		
3)	8	34.8	9	12.5	1	4 4	6	11 1	6	22.2	4	23.5	12	37.5	7	53 9	2		—		8	61.5	—	
4)	3	13.0	8	11 1	1	4 4	6	11 1	3	11 1	4	23.5	9	28 1	7	53.9	—		—		4	30.8	—	
6)	9	39 1	12	16.7	7	30.4	15	27.8	7	25 9	8	47 1	17	53 1	7	53.9	2		—		10	76.9	—	
7)	7	30.4	9	12.5	6	26.1	14	25 9	5	18.5	8	47 1	11	34 4	7	53 9	1		—		11	84.6	—	
8)	7	30.4	6	8.3	3	13 0	5	9.3	6	22.2	3	17.7	11	34 4	3	23 1	1		—		6	46.2	—	
9)	5	21.7	6	8.3	5	21.7	5	9.3	4	14.8	3	17.7	6	18.8	3	23 1	1		—		8	61.5	—	
14a)	13	56.5	3	4.2	12	52.2	11	20.4	17	63.0	1	5.9	18	56.3	1	7.7	1		—		8	61.5	—	
14b)	2	8.7	1	1 4	2	8.7	1	1 9	1	3.7	—		2	6.3	4	30.8	—		—		2	15 4	—	
14c+d)	1	4 4	1	1 4	—	—	—		—		—		1	3 1			—		—		—		—	
17)	8	34 8	16	22.2	9	39 1	13	24 1	6	22.2	3	17.7	11	34 4	7	53 9	1		—		3	23 1	—	
1)	6	26.1	9	12.5	6	26.1	10	18.5	4	14.8	4	23.5	9	28.1	1	7.7	2		—		4	30.8	—	

The numbers i the left column correspond to the question numbers in the MRC questionnaire.

TABLE 32

Sputum Volumes in Different Smoking Categories

London

	Nil		0-		2+		N.R.	
	No.	/	No.	/	No.	/o	No.	/
Non-smokers	3	42.9	—	—	1	14.3	3	42.9
Ex-smokers	9	42.9	4	19.0	6	28.6	2	9.5
1 14 g/day	19	41.3	4	8.7	14	30.4	9	19.6
15-24 g/day	18	30.5	8	13.6	24	40.7	9	15.2
25+ g/day	5	29.4	—	—	10	58.8	2	11.8

Bergen

	No.	%	No.	/	No.	/	No.	/
	Nil		0-		2+		N.R.	
Non-smokers	9	90.0	—	—	1	10.0	—	—
Ex-smokers	15	75.0	1	5.0	4	20.0	—	—
1 14 g/day	65	51.6	17	13.5	38	30.[illegible]	6	4.8
15-24 g/day	11	36.7	3	10.0	14	46.6	2	6.7
25+ g/day	2	(67.7)	—	—	1	(33.3)	—	—

latory function, but that the production of a larger amount of sputum is accompanied by a marked reduction in respiratory capacity. These findings are consistent with those of Fletcher & Tinker (1960) in a study of transport workers in London. The PRF values are consistently lower in the British sample than in corresponding volume-categories in the Norwegian sample, suggesting that factors other than those determining the production of phlegm may influence the lung function as assessed by measuring the PRF

The chief differences found between men in the London and the Bergen sample when compared in corresponding tobacco consumption categories, are that the British men

TABLE 33

Relationship between Peak Respiratory and Sputum Volumes

(PRF standardized to age 40)

	London		Bergen	
	No.	PRF	No.	PRF
Nil	61	485.7	107	539.6
0	10	479.7	18	544.9
2+	54	437.8	56	479.3
Not ret.	25	449.3	8	504.9
	150		189	

In this table the men who returned sputum specimens classified as saliva have been included in the 'nil' group.

TABLE 31

Peak Respiratory Flow in Different Smoking Categories

(PFR standardized to age 40)

	London			Bergen			
	No.	PRF litre/min.		No.	PRF litre/min.		L/B %
Non-smokers	7	457.2		10	587.0		78 %
Ex-smokers	21	469.9		20	563.4		83 %
1-14 g/day	46	456.3		126	514.8		89 %
15-24 g/day	59	447.3	443.2	30	492.6	499.6	90 %
25+	17	428.2		3	569.0		
	150			189			

from both agricultural and industrial populations in England & Wales. Neither Fletcher *et al* (1959) nor Higgins (1959) found any significant difference between light and heavy smokers in ventilatory capacity. Higgins (1959) suggested that this rather surprising finding may be due to changes in smoking habits as the lung efficiency becomes impaired. In other words, a selection out of the higher categories for present tobacco consumption by persons with impaired lung function might account for the absence of any significant trend in the ventilatory capacity with increasing tobacco consumption. This hypothesis can only be tested by accurate information on previous changes in tobacco consumption to see if smokers getting serious respiratory manifestations reduce the amount of tobacco smoked. Assuming that this is so, the trend found in the Norwegian sample in this study may reflect a lower prevalence of serious respiratory symptoms in corresponding consumption categories, compared with British samples, causing less transfer of men from higher to lower consumption categories, and consequently less tendency to level out differences in ventilatory capacity among smokers.

In Table 32 the production of sputum has been related to the different levels of tobacco consumption. The relatively high proportion of sputum containers not returned in the British sample necessitates caution in drawing conclusions from these data, but it seems as if the phlegm production in the two samples is quite similar in corresponding smoking categories. Table 33 gives the mean PRF (standardized to age 40) in relation to sputum volumes. In both samples there is a marked decline in PRF with increasing phlegm production but with little difference, however, between the men without any phlegm and those producing less than 2 cc the first hour after getting up. It seems as if minor phlegm production may be of little value as an indirect index of impaired venti-

TABLE 32

Sputum Volumes in Different Smoking Categories

London

	Nil		0-		2+		N.R.	
	No.	%	No.	%	No.	%	No.	%
Non-smokers	3	42.9	–	–	1	14.3	3	42.9
Ex-smokers	9	42.9	4	19.0	6	28.6	2	9.5
1 14 g/day	19	41.3	4	8.7	14	30.4	9	19.6
15-24 g/day	18	30.5	8	13.6	24	40.7	9	15.2
25+ g/day	5	29.4	–	–	10	58.8	2	11.8

Bergen

	No.	%	No.	%	No.	%	No.	%
	Nil		0-		2+		N.R.	
Non-smokers	9	90.0	–	–	1	10.0	–	–
Ex-smokers	15	75.0	1	5.0	4	20.0	–	–
1 14 g/day	65	51.6	17	13.5	38	30.2	6	4.8
15-24 g/day	11	36.7	3	10.0	14	46.6	2	6.7
25+ g/day	2	(67.7)	–	–	1	(33.3)	–	–

latory function, but that the production of a larger amount of sputum is accompanied by a marked reduction in respiratory capacity. These findings are consistent with those of Fletcher & Tinker (1960) in a study of transport workers in London. The PRF values are consistently lower in the British sample than in corresponding volume-categories in the Norwegian sample, suggesting that factors other than those determining the production of phlegm may influence the lung function as assessed by measuring the PRF.

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Relationship between Peak Respiratory and Sputum Volumes

(PRF standardized to age 40)

	London		Bergen	
	No.	PRF	No.	PRF
Nil	61	483.7	107	539.6
0	10	479.7	18	544.9
2+	54	407.8	56	479.3
Not ret.	25	449.3	8	504.9
	150		189	

In this table the men who returned sputum specimens classified as saliva have been included in the 'nil' group.

tend to have more chest illnesses and lower PRF readings. As only the amount of tobacco smoked and not the type of tobacco product has been taken into account in these comparisons, this feature might be caused by the higher proportion of pure cigarette-smokers in the British sample. Also the finding of a much higher proportion of men rolling their own cigarettes in the Norwegian sample compared with the British one, raises the question of whether the differences observed may be due to qualitative differences in the smoke from manufactured and hand-rolled cigarettes In this study the numbers in each sub-group are getting too small for comparisons to be made when the cigarette-smokers are divided into those smoking manufactured and hand rolled cigarettes. In both samples the numbers of pure pipe-smokers and of mixed pipe/cigarette-smokers are also too small to be compared. Differences found between groups of mixed smokers would be difficult to interpret, as one is usually without information on how much of the total consumption is consumed as cigarettes. This group is probably very heterogeneous even within the same population as far as tobacco products are concerned.

It is quite conceivable that there are important differences in the pharmacological effect on the lung of different kinds of tobacco-smoke Little is known, however of the importance of this factor in relation to the respiratory symptoms with which we are concerned in this study Higgins (1959) found that pipe-smokers had fewer symptoms than cigarette smokers, but that they were not as free from symptoms as non smokers, concluding that they form an intermediate group possibly closer to the smokers than is usually believed Olsen & Gilson (1960) investigating the lung function in men smoking different tobacco products found that the cigarette smokers were most affected the cigar smokers least, and the pipe-smokers intermediate with regard to ventilatory capacity

The qualitative difference in tobacco consumption between the two samples in the present study seems to be of little importance in determining the prevalence of symptoms like cough and phlegm which is the same in men smoking the same amount of tobacco One can hardly assume that these qualitative differences can account for all of the difference observed in the prevalence of chest illnesses and in ventilatory capacity in corresponding consumption groups. A more likely explanation of the observed differences in these more serious symptoms seems to be the difference between the samples in their exposure to atmospheric pollution The men in Bergen are working and living in an unpolluted area, whereas the men in London are exposed to comparatively high concentrations of air pollution. This hypothesis is supported by the observation made in a number of studies in the U.K. (Higgins 1957 Higgins *et al* 1959 College of General Practitioners 1960) of a rural/urban gradient in the more severe symptoms of cardio-respiratory disease and small differences in the prevalence of minor symptoms.

The findings of a lower mean PRF in London than in Bergen even in the

part of the samples without cough and phlegm, may suggest that atmospheric pollution to some extent also affects the lung function in persons without symptoms attributable to bronchial irritation. Olsen & Gilson (1960) assume, however that measurements of ventilatory capacity and gas distribution are likely to be a rough measure of the severity of bronchial irritation. Larger samples of *non-smokers living in polluted and unpolluted* areas would probably have to be compared in order to establish whether the lung function is reduced by exposure to air pollution independent of the coincident effect of tobacco-smoke. This problem deserves attention in future research.

The possible interaction of tobacco-smoke and atmospheric pollution in the causation of disease is, however of greater public health importance, as the majority of the population is addicted to tobacco-smoking. It is medically quite conceivable that once the respiratory tract has been damaged by the irritative effect of tobacco-smoke, it becomes more susceptible to a deleterious effect of other irritants as for example polluted air and that such additional factors are of great importance in the evolution of a minor respiratory syndrome' — caused chiefly by smoking — into a disabling and fatal cardio-respiratory disease. This hypothesis would also explain the apparent inconsistency between the similarity in the prevalence of most respiratory symptoms in these samples from England & Wales and Norway and the large differences in recorded morbidity and mortality in the general population in the two countries.

Summary and conclusions (Part II)

From the examination of available statistical data described in the first part of this study it was concluded (p 62) that surveys in different countries were desirable in order to elucidate further the problems of international differences in the prevalence of chronic cardio-respiratory diseases. Male transport workers aged 40-59 in Bergen, Norway and in London have been studied and compared for prevalence of respiratory symptoms, chest illnesses, ventilatory capacity and smoking habits.

In corresponding age-groups a higher prevalence of most respiratory symptoms is found in London, and the peak respiratory flow (PRF) is lower in the London sample. No difference is found in past chest illness experience, but a higher prevalence of sickness absence within the last 3 years ascribed to bronchitis is found among the men aged 50-59 in London. Recurrent chest illnesses, however are found to be as common in the Norwegian as in the British sample. Data on retirements and deaths in the two occupational samples have been discussed, and it is concluded that disparities in this respect may *invalidate* the comparability of sickness rates in working populations of middle aged males.

The differences observed between the two samples in the prevalence of respira-

tory symptoms and lung function can hardly be explained by differences in anthropometric measurements and socio-economic factors. The samples are found to differ both qualitatively and quantitatively in their smoking habits. There is a higher proportion of pure cigarette-smokers among the men in London, and the average consumption of tobacco is higher Comparing the rates in corresponding consumption categories, it is found that the differences observed between the samples in the prevalence of cough and production of phlegm, may be explained entirely by disparities in levels of tobacco consumption. The differences observed in the prevalence of more serious symptoms and in ventilatory capacity are not eliminated by standardizing for smoking. It is suggested that these disparities may be explicable on the basis of the considerable differences between the groups in their exposure to atmospheric pollution

Discussing the results of the present study and of studies in the epidemiology of chronic bronchitis published by other workers, it is concluded that tobacco-smoking may be of decisive importance in determining the prevalence of a minor respiratory syndrome' but that an additional effect of atmospheric pollution is of major importance in the transition of this syndrome into a disabling and fatal chronic cardio-respiratory disease.

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I INTRODUCTION

It is the purpose of this study to present data obtained from a survey of human serum proteins in health and disease. The advantages of membrane electrophoresis in the analysis and application of protein fractions for clinical purposes have long been recognized, and several publications describing paper electrophoretic protein aberrations due to disease have appeared (Gutman, 1948 Fisher 1953 Flynn, 1954 Jencks, Smith and Durrum, 1956 Sunderman and Sunderman, 1957 Owen, 1958 Ogryzlo, Maclachlan, Dauphinee and Fletcher 1959 Putnam, 1960) Such reports have described both qualitative and quantitative protein differences between pathological and normal sera. Frequently however quantitative estimations have been based on simplifying assumptions, such as uniform dye-binding capacities of separated protein fractions, afterwards shown to be untenable (Sunderman and Sunderman, 1959 Yeoman, 1959 Brackenridge 1960a) As result, while comparative protein analyses in disease with respect to health are useful and informative reliance on absolute values in such cases must be subject to careful scrutiny

A recently described rapid quantitative method of serum protein analysis by cellulose acetate electrophoresis, which allow for heterogeneous dye-binding capacities of fractions (Brackenridge 1960 b,) is well suited to a survey of comparative and absolute differences. As such, the present study is the first to incorporate cellulose acetate electrophoresis as far as the authors are aware Another consideration stems from the fact that few attempts have been made in previous surveys to subdivide large numbers of cases, and to allow for differing stages of severity and pathogenesis. The clinical criteria according to which disease states are classified, and sometimes further subdivided, have not always been adequately described in the past. In the present investigation data are presented with supporting biochemical and pathological details to strengthen description and subdivision of cases. In a limited number of cases comparison of electrophoretic results with certain biochemical assays, such as phospholipid-cholesterol ratio and hexosamine content, has been made.

Three further reasons for undertaking another comprehensive study may be suggested. Firstly few if any of earlier surveys can claim to include the whole field of human disease rather consciously or unconsciously there is a trend to emphasize some disorders to the exclusion of others. In the present publication, there is a preponderance of infectious, neoplastic cardiovascular and haematological diseases, with a deficiency in venereal, neurological, dermatological, mental, endocrine, and metabolic diseases. It is therefore only partly repetitive of previous work.

Secondly numerous individual publications based on widely differing electrophoretic techniques have described protein abnormalities incurred by narrowly defined disease states. It is essential

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Thirdly knowledge of isolated serum protein constituents has increased enormously in recent years, thus necessitating the evaluation and interpretation of results in the light of recent developments.

The present survey was undertaken for the purpose of investigating the major types of response of the serum proteins to the various pathological stimuli rather than describing individual disease patterns Our experience suggests that this course is more helpful and meaningful as a diagnostic and prognostic aid in certain disorders.

Material

Practically all cases were admitted to Royal Perth Hospital or King Edward Memorial Hospital for Women during the year 1960. Blood was collected not later than two days after admission and the electrophoretic result kept until a definite diagnosis was obtained. In calculating the normal ranges of protein fraction concentrations blood was obtained from healthy hospital staff and their relatives. Selection of normal persons was carefully controlled by matching the sex and age distributions of the pathological cases. In all analyses serum was used for electrophoresis within three days of venepuncture, any storage being at 4° C in a refrigerator.

The mean values of each of the protein fractions albumin (A), α_1-globulin (α_1-G), α_2-globulin (α_2-G), β-globulin (β-G), γ-globulin (γ-G), total globulin (TG) and total protein (TP) are shown in Table I. The figures are based on one hundred presumably healthy white Australian persons of mean age 46 years and female to male ratio 1.27. The normal ranges of the approximately normally distributed fractions are defined as $\pm$ 2 standard deviations from the means so that 95% of cases fall within them. The results agree well with previously published data obtained with cellulose acetate electrophoresis (Brackenridge, 1960 c). Virtually no variation of mean values with sex was observed, but there was a small significant trend with age in which the albumin tended to fall and the major lipoprotein fractions (α_1- and β-globulins) rose. This confirms previous reports (Jencks, Smith and Durrum, 1956; Brackenridge, 1960 c).

Of 1,260 cases examined, precisely one third was rejected on one or more of the following grounds:

Table I. Relation of serum protein concentrations (in grams per 100 ml) to standard deviations from the normal mean

Standard deviation	A	α_1-G	α_2-G	β-G	γ-G	TG	TP
−11	0.68	—	—	—	—	—	—
−10	0.99	—	—	—	—	—	2.70
−9	1.30	—	—	—	—	—	3.15
−8	1.61	—	—	—	—	—	3.60
−7	1.92	—	—	—	—	—	4.05
−6	2.23	—	—	—	—	—	4.50
−5	2.54	—	—	0.38	0.25	1.71	4.95
−4	2.85	0.17	0.35	0.49	0.43	1.99	5.40
−3	3.16	0.20	0.45	0.60	0.61	2.27	5.85
−2	3.47	0.23	0.55	0.71	0.79	2.55	6.30
−1	3.78	0.26	0.65	0.82	0.97	2.83	6.75
M[1]	4.09	0.29	0.75	0.93	1.15	3.11	7.20
+1	4.40	0.32	0.85	1.04	1.33	3.39	7.65
+2	4.71	0.35	0.95	1.15	1.51	3.67	8.10
+3	5.02	0.38	1.05	1.26	1.69	3.95	8.55
+4	5.33	0.41	1.15	1.37	1.87	4.23	9.00
+5	—	0.44	1.25	1.48	2.05	4.51	9.45
+6	—	0.47	1.35	1.59	2.23	4.79	9.90
+7	—	0.50	1.45	1.70	2.41	5.07	10.35
+8	—	0.53	1.55	1.81	2.59	5.35	10.80
+9	—	0.56	1.65	1.92	2.77	5.63	11.25
+10	—	0.59	1.75	2.03	2.95	5.91	11.70
+11	—	0.62	1.85	—	3.13	6.19	12.15
+12	—	0.65	1.95	—	3.41	6.47	—
+13	—	0.68	2.05	—	3.59	—	—
+14	—	0.71	2.15	—	3.77	—	—
+15	—	0.74	—	—	—	—	—
+16	—	0.77	—	—	—	—	—

[1] Mean normal value. Limits of normal range.

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Material

Practically all cases were admitted to Royal Perth Hospital or King Edward Memorial Hospital for Women during the year 1960 Blood was collected not later than two days after admission and the electrophoretic result kept until a definite diagnosis was obtained. In calculating the normal ranges of protein fraction concentrations blood was obtained from healthy hospital staff and their relatives. Selection of normal persons was carefully controlled by matching the sex and age distributions of the pathological cases. In all analyses serum was used for electrophoresis within three days of venepuncture, any storage being at 4 C in a refrigerator

The mean values of each of the protein fractions albumin (A) α_1-globulin (α_1-G) α_2-globulin (α_2-G) β-globulin (β-G) γ-globulin (γ-G) total globulin (TG) and total protein (TP) are shown in Table I The figures are based on one hundred presumably healthy white Australian persons of mean age 46 years and female to male ratio 1.27 The normal ranges of the pproximately normally distributed fractions are defined as ± 2 standard deviations from the means so that 95 % of cases fall within them. The results agree well with previously published data obtained with cellulose acetate electrophoresis (Brackenridge, 1960 c) Virtually no variation of mean values with sex was observed, but there was a small significant trend with age in which the albumin tended to fall and the major lipoprotein fractions (α_1- and β-globulins) rose. This confirms previous reports (Jencks, Smith and Durrum, 1956 Brackenridge, 1960 c)

Of 1,260 cases examined, precisely one third was rejected on one or more of the following grounds

Table I Relation of serum protein concentrations (in grams per 100 ml) to standard deviations from the normal mean

Standard deviation	A	α_1-G	α_2-G	β-G	γ-G	TG	TP
−11	0.68	—	—	—	—	—	—
−10	0.99	—	—	—	—	—	2.70
− 9	1.30	—	—	—	—	—	3.15
− 8	1.61	—	—	—	—	—	3.60
− 7	1.92	—	—	—	—	—	4.05
− 6	2.23	—	—	—	—	—	4.50
− 5	2.54	—	—	0.38	0.25	1.71	4.95
− 4	2.85	0.17	0.35	0.49	0.43	1.99	5.40
− 3	3.16	0.20	0.45	0.60	0.61	2.27	5.85
− 2	3.47	0.23	0.55	0.71	0.79	2.55	6.30
− 1	3.78	0.26	0.65	0.82	0.97	2.83	6.75
M	4.09	0.29	0.75	0.93	1.15	3.11	7.20
+ 1	4.40	0.32	0.85	1.04	1.33	3.39	7.65
+ 2	4.71	0.35	0.95	1.15	1.51	3.67	8.10
+ 3	5.02	0.38	1.05	1.26	1.69	3.95	8.55
+ 4	5.33	0.41	1.1	1.37	1.87	4.23	9.00
+ 5	—	0.44	1.25	1.48	2.05	4.51	9.45
+ 6	—	0.47	1.35	1.59	2.23	4.79	9.90
+ 7	—	0.50	1.45	1.70	2.41	5.07	10.35
+ 8	—	0.53	1.55	1.81	2.59	5.35	10.80
+ 9	—	0.56	1.65	1.92	2.77	5.63	11.25
+10	—	0.59	1.75	2.03	2.95	5.91	11.70
+11	—	0.62	1.85	—	3.13	6.19	12.15
+12	—	0.65	1.95	—	3.41	6.47	—
+13	—	0.68	2.05	—	3.59	—	—
+14	—	0.71	2.15	—	3.77	—	—
+15	—	0.74	—	—	—	—	—
+16	—	0.77	—	—	—	—	—

Mean normal value. Limits of normal range.

Table II Distribution of 850 cases among 14 classes of disease

Class of disease	Number of cases
Infectious	86
Neoplastic	146
Degenerative cardiovascular	100
Mental	48
Asthma	18
Dermatological	13
Haematological	114
Gastrointestinal	44
Renal	31
Metabolic	15
Obstetric	72
Endocrine	35
Hepatic	40
Rheumatic	70

(1) one or more diseases in a patient unrelated to that under which the case was primarily classified

(2) cases treated or transfused prior to electrophoresis. (A limited number of such cases has been included for comparison with untreated cases, *vide infra*)

(3) patients who were not drawn from a white population this is a precaution against possible genetic effects on proteins (Curnow 1957 Owen 1958)

(4) cases in which a definite clinical diagnosis was not obtained

(5) children under fourteen years of age.

The remaining cases were divided into fourteen primary classes of disease, the distribution being as shown in Table II It will be apparent that this system of classification is sometimes arbitrary thus cases of viral hepatitis have been included under hepatic rather than infectious disease.

In the presentation of data the following outline has generally been observed

(1) Establishment of criteria for subdivision of cases within initial classes of disease

(2) Statement of supporting biochemical tests when available

(3) Presentation of mean values of protein fractions, distribution of cases in terms of standard deviations from normal, comparison with normal ranges, and conclusions drawn

(4) Comparison of such results with previous reports,

(5) General discussion and relation of protein abnormality to class of disease with possible clinical significance

In assessing whether mean values of protein fractions in disease differed significantly from those of the normal controls, a novel distribution table has been favoured to statistical procedures. All possible concentrations of the seven protein fractions have been expressed as positive or negative integers representing one standard deviation Thus if the value of a fraction falls within the range specified by $\pm$ n standard deviations from the mean of the normal range it is assigned a value of $\pm$ n, the sign depending on whether it lies above or below the normal mean In this way the mean value and distribution of cases can be readily tabulated for each protein fraction in a particular subdivision or class of disease The key to this method of presentation is found in Table I The system is not used in classes of disease having less than ten cases, or in those disorders involving abnormal serum proteins presumed to be absent in normal humans. It is considered that this method of presentation expresses the central tendency in a more readily visualized form than the statistical *t* test

Methods

Electrophoresis. The method of quantitative analysis of serum protein fractions by cellulose acetate electrophoresis and elution of stained bands has been fully described elsewhere (Brackenridge, 1960 b, c, d)

Normal Ranges. Most of the following supporting methods were performed, with or without modification, as described by Varley (1958) References to the exceptions are given in the text. The normal ranges determined in the laboratories of the hospital are as follows.

Hexosamine 84 to 132 mg per 100 ml serum.

Total Cholesterol 150 to 290 mg per 100 ml serum.

Phospholipid-Cholesterol Ratio 0 85 to 1 18.

Serum Glutamic Oxaloacetic Transaminase 0 to 40 units.

Erythrocyte Sedimentation Rate (Westergren) males under 10 females under 15 mm per hour

Xylose Absorption 4 1 to 6.2 g per 5 hours.

Serum Amylase 70 to 200 units.

Carotene Over 70 μg per 100 ml serum.

Urea 15 to 40 mg per 100 ml blood.

Protein-Bound Iodine 3 to 8 μg per 100 ml serum.

Serum Alkaline Phosphatase 3 to 13 King-Armstrong units.

Bilirubin Less than 1.0 mg per 100 ml serum.

Thyroglobulin Antibody Agglutination Titre Not greater than 1 250

Anti-streptolysin 0 Titre Not greater than 150 units.

Rose and Ball Titre Not greater than 1 64

C-Reactive Protein Negative.

Iron Males 80—180 females 60—160 μg per 100 ml serum.

Clinical notes

Eighty-six cases of infectious diseases were classified within six subdivisions: acute bacterial, chronic bacterial, viral, infectious mononucleosis, parasitic, and sarcoidosis. The latter has been arbitrarily included here for convenience. Table III shows the distribution of cases.

All cases were selected on the basis of definite clinical diagnosis. With two exceptions, the acute *infectious cases all* gave a short history of illness. Clinical diagnosis was supported by various laboratory findings. Thirty five of the cases showed polymorpholeucocytosis (white cell count over 10 000 per cubic millimetre). All the pneumonia cases had radiological evidence of various degrees of pneumonic consolidation and in eight cases there was additional pleural effusion. Organisms were isolated in twenty eight cases.

The chronic cases had at least a four week history of disease; in many cases it dated back several months. Diagnosis was supported by blood cultures or in cases of osteomyelitis, melioidosis and otitis media, organisms were isolated from pus. In one fatal case of subacute bacterial endocarditis autopsy revealed characteristic vegetations on the cardiac valves. Five of the tuberculosis cases were of long standing while seven were recently detected. All were active and had a positive sputum culture for acid fast bacilli. Several had been previously treated and some were under antituberculous therapy at the time of the test. One case of tabes dorsalis yielded a positive Wassermann reaction on repeated serological examination and the cerebrospinal fluid gave the characteristic Lange curve.

The diagnosis of one case of psittacosis was confirmed by serological tests. In the cases of lymphocytic meningitis no organisms were isolated. In one the clinical findings were supported by a raised cerebrospinal fluid protein content of 127 mg

Table III Distribution of cases in infectious diseases

Disease	Number of cases	Total
Acute bacterial infection		53
Abscess	5	
Infected haematocele of scrotum	1	
Furunculosis	1	
Generalized peritonitis	1	
Epididymo-orchitis	1	
Gonococcal infection	1	
Pneumonia	43	
Chronic bacterial infection		25
Chronic otitis media	3	
Chronic discharging sinus	1	
Subacute bacterial endocarditis	4	
Osteomyelitis	3	
Tabes dorsalis	1	
Pulmonary tuberculosis	10	
Renal tuberculosis	1	
Tuberculous lymphadenitis	1	
Melioidosis	1	
Viral infection		3
Psittacosis	1	
Lymphocytic meningitis	2	
Infectious mononucleosis	3	3
Parasitic infestation	1	1
Malaria	1	
Sarcoidosis	1	1
	Total	*86*

Table IV Distribution, in standard deviations from the normal mean, and mean values of serum protein fractions in infectious diseases

Acute Infection

Fraction	Standard deviations from normal mean																							Mean value
	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	
A	1	—	6	7	11	10	8	6	3	1	—	—	—	—	—	—	—	—	—	—	—	—	—	2.91
α-G	—	—	—	—	—	—	—	—	1	3	4	5	7	8	4	3	5	5	3	4	—	2	1	0.47
α_2-G	—	—	—	—	—	—	—	—	1	1	2	9	13	8	7	5	6	—	—	—	—	—	—	1.22
β-G	—		—	—	—	1	1	3	4	5	16	15	6	2	—	—	—	—	—	—	—	—	—	1.10
γ-G	—	—	—	—	—	1	3	7	10	11	11	5	1	2	—	2	—	—	—	—	—	—	—	1.27
TG	—		—	—	—	—	—	—	5	4	2	10	14	8	8	—	2	—	—	—	—	—	—	4.06
TP	—	—	—	—	1	5	4	8	11	15	7	1	1	—	—	—	—	—	—	—	—	—	—	6.97

Chronic infection

Fraction	Standard deviations from normal mean																							Mean value
	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	
A	—	1	1	5	2	4	4	3	3	2	—	—	—	—	—	—	—	—	—	—	—	—	—	3.08
α-G	—	—	—	—	—	—	—	—	—	6	5	4	3	1	2	2	2	—	—	—		—	—	0.38
α-G	—	—	—	—	—	—	—	1	1	3	4	5	3	3	3	2	—	—	—	—	—	—	—	1.04
β-G	—	—	—	—	—	—	—	1	5	5	3	6	3	2	—	—	—	—	—	—	—	—	—	1.08
γ-G	—	—	—	—	—	—	—	—	—	2	5	5	6	1	2	2	2	—	—	—	—	—	—	1.77
TG	—	—	—	—	—	—	—	—	—	1	1	6	8	2	2	—	3	2	—	—	—	—	—	4.27
TP	—	—	—	—	—	1	2	1	7	9	1	1	1	2	—	—	—	—	—	—	—	—	—	7.33

Mean alues for viral infection, infectious mononucleosis, and parasitic infestation

Fraction	Viral infection	Infectious mononucleosis	Malaria
A	3.41	3.49	3.58
-G	0.44	0.48	0.33
α_2-G	0.91	0.78	0.61
β-G	1.32	1.39	[illegible]
γ-G	1.52	1.56	1.56
TG	4.18	4.21	3.30
TP	7.60	7.70	6.96

Mean value

per 100 ml and by the large number of leucocytes, of which 95 % were lymphocytes. In the other, 70 % of leucocytes were lymphocytes.

Of the remainder three cases of infectious mononucleosis showed a positive Paul Bunnell test The single malarial patient had been treated during the previous four months *plasmodium vivax* was identified in blood films soon after admission. One case of sarcoidosis was supported by scalene lymph node biopsy

Results

In Table IV the means and distributions in terms of standard deviations from normal of the protein fractions are given for five subdivisions.

Acute Infection. The serum protein changes consist of a moderate decrease in albumin accompanied by a marked increase in both the α-globulins. In ten of 43 cases of pneumonia the γ-globulins were elevated. Of these, two had a ten-day history before blood collection three had large bilateral pleural effusions, and in one case of staphylococcal aetiology the possibility of lung abscess was not excluded In four cases nothing unusual was observed to account for the raised γ-globulins.

The β-globulin mean falls within the high normal range and the γ-globulin mean is only slightly higher than normal The mean of the total proteins remains within the normal range. These observations are in general agreement with previous reports by Jencks Smith and Durrum (1956) Sunderman and Sunderman (1957) and Seibert Seibert Atno and Campbell (1947) However these authors fail to emphasize the significant increase in the α_1-globulin fraction The mean hexosamine value of 144 mg per 100 ml obtained in thirteen cases of pneumonia indicates a moderate increase in acute infection. It is probably a reasonable index of increased polysaccharide content in serum previously described by Seibert Seibert Atno and Campbell (1947) The mean phospholipid-cholesterol ratio in these thirteen cases was 1 13 which is within the normal range

Chronic Infection The electrophoretic pattern reveals a moderate decrease of albumin and slight increases of α and γ-globulins. Similar findings have been published for chronic infection (Mackay and Volwiler 1954 Sunderman and Sunderman 1957) and tuberculosis (Baldwin and Iland, 1953)

Viral Infection. Due to the small number of cases it is difficult to draw conclusions however a tendency towards raised γ-globulins is apparent.

Infectious Mononucleosis The findings in agreement with earlier work (Sterling 1949) were a low normal albumin, markedly raised α-globulins, normal α_2-globulin markedly raised β-globulin and slightly raised γ-globulin fractions It is interesting to note the very high β-globulins and the consistently normal α globulins. It is known that the heterophilic antibody is carried in the γ-globulin fraction but because of the small number of cases no correlation of antibody titre with γ-globulin concentration is possible

Malaria Except for a slightly raised γ-globulin fraction the electrophoretic pattern was normal.

Sarcoidosis The patient a 31 year-old male, presented with a ten-day history of pleuritic chest pain general malaise fatigue and intermittent rigor On examination there was marked sternal tenderness. Chest X ray showed increased

mediastinal shadow greater on the right side than the left, with otherwise clear lung fields. Liver function tests were normal. The Paul-Bunnell test was negative. Sputum and gastric aspirate failed to grow acid-fast bacilli. The following report on a scalene node biopsy was made "Throughout the cortex and medulla there are sharply circumscribed groups of epithelioid cells and giant cells. Caseation is absent in the centre of these aggregates and a Ziehl-Neelsen stain has revealed no acid-fast bacilli. Histiocytic proliferation is seen in the sinuses."

Table V described the electrophoretic and hexosamine results on admission and three weeks later It can be seen that the α- and β-globulins respond more rapidly to the acute phase than the albumin and γ-globulin fractions. With the onset of the chronic phase, there is a marked depletion in albumin accompanied by a slight increase in the γ-globulins, while the intermediate globulins decrease slightly

The appreciable effect of the course of sarcoidosis on the electrophoretic results may account for the lack of agreement in the literature on the serum protein pattern. It underlines the importance of co-

Table V Effect of course of disease on serum protein fractions and hexosamine level in sarcoidosis

Estimation	Admission	3 weeks later
A	4.20	3.00
α_1-G	0.64	0.46
α_2-G	1.31	1.23
β-G	1.84	1.62
γ-G	1.05	1.25
TG	4.84	4.56
TP	9.04	7.56
Hexosamine	150	190

ordinating the clinical and electrophoretic findings. Jencks, Smith and Durrum (1956) and Seibert Seibert, Atno and Campbell (1947) reported a decrease in albumin and a significant increase in γ-globulins with no alteration in the α- and β-globulins. Sunderman and Sunderman (1957) describe a unique and characteristic mean pattern in nine cases of Boeck's sarcoid involving a steplike increase in α_2- β- and γ-globulins with a slight decrease in albumin. A more recent study (Ogryzlo, Maclachlan, Dauphinee and Fletcher 1959) reports only one raised γ-globulin fraction out of nine sarcoid cases.

Clinical notes

One hundred and forty-six cases of neoplastic diseases were classified into benign and malignant groups The latter was further subdivided into group 1 (neoplasms confined to the organ of origin) and group 2 (of lymph node or distant organ metastasis) Table VI gives the distribution and sites of the various lesions. Mider Alling and Morton (1950) analysing 222 cases of neoplastic diseases failed to find significant electrophoretic differences between various anatomical sites. Therefore in this study only the severity of the cases was compared and considered for statistical purposes.

Table VI Relation of type or primary site of carcinoma with number and classification of cases

Type or site	Benign	Malignant 1	Malignant 2	Total
Basal cell	—	3	—	3
Keratoacanthoma	1	—	—	1
Squamous cell	—	5	5	10
Melanoma of skin	—	1	2	3
Breast	1	5	17	23
Thyroid	—	—	1	1
Astrocytoma	—	1	—	1
Oesophagus	—	2	2	4
Stomach	—	3	4	7
Small bowel	—	—	1	1
Colon	—	—	6	6
Sigmoid	—	1	3	4
Rectum	3	4	5	12
Pancreas	—	—	9	9
Gall bladder	—	—	2	2
Liver	—	—	1	1
Bladder	1	1	4	6
Prostate	1	1	4	6
Vulva	—	—	2	2
Cervix uteri	—	2	7	9
Uterus (body)	—	—	1	1
Ovary	—	1	5	6
Chorion epithelium	—	1	1	2
Larynx	—	3	2	5
Bronchus	—	—	9	9
Ewing tumour	—	1	—	1
Carcinomatosis of undiagnosed primary sit	—	—	11	11
Total	7	35	104	146

In all cases the clinical diagnosis was supported by pathological evidence obtained by biopsy or following operative procedures. In fatal cases, autopsy reports were taken into consideration. With the exception of eleven cases with secondary carcinomatous deposits having unconfirmed primary sites, the site of origin was established in all cases and confirmed by pathological examination

Results

The results of electrophoretic analyses of the three groups are shown in Table VII

Benign Neoplasia Analysis of the mean of seven cases revealed a normal electrophoretic pattern for benign neoplasia.

Malignant Neoplasia (Group 1) Confinement of tumours to the organ of origin resulted in only one abnormality namely a slight decrease in the albumin concentration insufficient to lower the total protein level below the normal range.

Malignant Neoplasia (Group 2) Secondary infiltrations produced a marked decrease in albumin a marked increase in α_1-globulins and a slight increase in α globulins. Means of the β- and γ-globulin fractions fell within the normal

Table VII Distribution, in standard deviations from the normal mean, of serum protein fractions in neoplastic disease

Group 1 malignant neoplasia

Fraction	Standard deviations from normal mean																									
	−11	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	+15
A	—	—	—	1	—	1	1	5	13	5	4	3	2	—	—	—	—	—		—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	—	—	—	—	1	7	11	5	6	4	1	—	—		—	—	—	—	—	—	—
α_2-G	—	—	—	—	—	—	—	—	1	2	7	12	8	5	—	—	—	—	—	—	—	—	—	—	—	—
β-G	—		—	—	—	—	—	—	2	6	8	6	6	3	1	1	1	—	1	—	—	—	—	—	—	—
γ-G	—	—	—	—	—	—	—	—	1	4	8	8	4	7	—	3	—	—	—	—	—	—	—	—	—	—
TG	—		—	—	—	—	—	—	—	3	6	10	14	6	4	2	—	—	—	—	—	—	—	—	—	—
TP	—	—	—	—	—	—	2	1	7	7	4	8	4	4	—	—	—	—	—	—	—	—	—	—	—	—

Group 2 malignant neoplasia

Fraction	Standard deviations from normal mean																									
	−11	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	+15
A		—	—	4	13	13	22	21	15	9	5	1	—		—	—	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—		—	—	—	—	—	2	3	7	9	14	10	12	20	8	5	3	5	1	5	1	—	1
α_2-G	—		—	—	—		—	—	—	5	11	12	12	24	16	11	12	2	—	1	—	—	—	—	—	—
β-G	—	—	—	—	—	1	1	—	5	12	17	21	14	19	7	4	2	—	—	—	1	—	—	—	—	—
γ-G		—	—	—	—	—	—	1	7	12	20	24	23	6	8	1	2	—	—	—	—	—	—	—	—	—
TG	—	—	—	—	—	—	—	1	1	3	9	10	22	22	21	10	3	1	1	—	—	—	—	—	—	—
TP	—	1	—	—	—		3	12	22	19	19	19	7	2	—	—	—	—	—	—	—	—	—	—	—	—

Mean values for benign, group 1 malignant, and group 2 malignant neoplasia

Fraction	Benign	Group 1 malignant	Group 2 malignant
A	3.35	3.46	2.84
α_1-G	0.31	0.53	0.45
α_2-G	0.85	0.82	1.00
β-G	0.98	1.01	1.03
γ-G	1.11	1.29	1.27
TG	3.24	3.45	2.73
TP	6.57	6.91	6.57

Mean value.

Clinical notes

One hundred and forty-six cases of neoplastic diseases were classified into benign and malignant groups. The latter was further subdivided into group 1 (neoplasms confined to the organ of origin) and group 2 (of lymph node or distant organ metastasis) Table VI gives the distribution and sites of the various lesions. Mider Alling and Morton (1950) analysing 222 cases of neoplastic diseases failed to find significant electrophoretic differences between various anatomical sites. Therefore in this study only the severity of the cases was compared and considered for statistical purposes.

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Melanoma of skin	—	1	2	3
Breast	1	5	17	23
Thyroid	—	—	1	1
Astrocytoma	—	1	—	1
Oesophagus	—	2		4
Stomach	—	3	4	7
Small bowel	—	—	1	1
Colon	—	—	6	6
Sigmoid	—	1	3	4
Rectum	3	4	5	12
Pancreas	—	—	9	9
Gall bladder	—	—	2	2
Liver	—	—	1	1
Bladder	1	1	4	6
Prostate	1	1	4	6
Vulva	—	—	2	2
Cervix uteri	—	2	7	9
Uterus (body)	—	—	1	1
Ovary	—	1	5	6
Chorion epithelium	—	1	1	2
Larynx	—	3	2	5
Bronchus	—	—	9	9
Ewing tumour	—	1	—	1
Carcinomatous of undiagnosed primary site	—	—	11	11
Total	7	33	104	146

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Table VII. Distribution, in standard deviations from the normal mean, of serum protein fractions in neoplastic diseases

Group 1 malignant neoplasia

Fraction	Standard deviations from normal mean																									
	−11	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	+15
A	—	—	—	1	—	1	1	5	15	5	4	3	2	—	—	—	—	—	—	—	—	—	—	—	—	—
α_1-G		—	—	—	—	—	—	—	—	1	7	11	5	6	4	1	—	—	—	—	—	—	—	—	—	—
α_2-G	—	—	—	—	—	—	—	—	1	2	7	12	8	5	—	—	—	—	—	—	—	—	—	—	—	—
β-G	—	—	—	—	—	—	—	—	2	6	8	6	6	3	1	1	1	—	1	—	—	—	—	—	—	—
γ-G	—	—	—	—	—	—	—	—	1	4	8	8	4	7	—	3	—	—	—	—	—	—	—	—	—	—
TG	—	—	—	—	—	—	—	—	—	3	6	10	4	6	4	2	—	—	—	—	—	—	—	—	—	—
TP	—	—	—	—	—	—	2	1	7	7	4	6	4	4	—	—	—	—	—	—	—	—	—	—	—	—

Group 2 malignant neoplasia

Fraction	Standard deviations from normal mean																									
	−11	−10	−9	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14	+15
A	—	—	—	4	13	13	22	21	15	9	5	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	—	—	—	—	2	3	7	9	14	10	12	20	8	5	3	3	1	5	1	—	1
α_2-G	—	—	—	—	—	—	—	—	—	3	11	12	12	24	16	11	12	2	—	1	—	—	—	—	—	—
β-G	—	—	—	—	—	1	1	—	5	12	17	21	14	19	7	4	2	—	—	—	1	—	—	—	—	—
γ-G	—	—	—	—	—	—		1	7	12	20	24	23	6	8	1	2	—	—	—	—	—	—	—	—	—
TG	—	—	—	—	—	—		1	1	3	9	10	22	22	21	10	3	1	1	—	—	—	—	—	—	—
TP	—	1	—	—	—		3	12	22	19	19	19	7	2	—	—	—	—	—	—	—	—	—	—	—	—

Mean values for benign, group 1 malignant, and group 2 malignant neoplasia

Fraction	Benign	Group 1 malignant	Group 2 malignant
A	3.53	3.46	2.84
α_1-G	0.31	0.33	0.43
α_2-G	0.83	0.82	1.00
β-G	0.99	1.01	1.03
γ-G	1.11	1.29	1.27
TG	3.24	3.45	2.73
TP	6.57	6.91	6.57

Mean value.

range. Thus the mean total globulin concentration *of this group was slightly* raised but the mean total protein remained inside normal limits.

These observations are in accordance with a large number of studies published in the literature (Mider Alling and Morton, 1950 Seibert Seibert, Atno and Campbell 1947 Jencks, Smith and Durrum, 1956 Sunderman and Sunderman, 1957) It is obvious that the alterations in the serum protein electrophoretic pattern in advanced malignancy are not specific for the disease because of the similarity to alterations occurring in acute infection. However the increase in the α_2-globulin fraction is usually relatively greater in acute infection.

In ten cases of advanced carcinoma, plasma hexosamine levels were estimated with a resulting mean of 143 mg per 100 ml. This agrees with the high hexosamine concentrations in cancer described by Weiden (1958) Winzler (1953) reported elevations in serum mucoprotein content from cancer patients of the same order of magnitude as those of pneumonia cases. Comparing these results with the present data it is concluded that the response of the body to acute infection and to neoplasia is essentially similar producing an increased serum mucoprotein concentration which is reflected in the marked increase in α-globulins. The reason for concomitant hypoalbuminaemia remains uncertain (Winzler 1953)

Thus far two broad types of pattern have been observed they may be classified in terms of the kinetics of new antibody formation. The first, the "immediate response pattern" may be defined as the result of those alterations incurred by the protein pool during the latent period of antibody response to the pathogenic agent. The second, the delayed response pattern may be defined as the result of those alterations incurred by the protein pool after the latent period of antibody response. The choice of γ-globulin production as the basis of differentiating immediate from delayed reactions is quite arbitrary and rests on the assumption that antibody response to pathogenesis is qualitatively similar to the biosynthesis of specific antibodies following antigenic administration. There is a latent period during which no antibody is formed (lasting about one week after injection) a rapid rise in γ-globulin and perhaps β-globulin concentrations within two to five days, followed by a period of slow decline of circulating antibody which can last for months. Electrophoretically hypoalbuminaemia and elevated α-globulin levels mark the immediate response pattern Further hypoalbuminaemia, a slackening in the elevation of α-globulins, raised γ- and possibly raised β- globulins mark the delayed response pattern. Examples of these two types are found in metastatic carcinoma (immediate response) and chronic infection (delayed response) Transition from the immediate to the delayed response pattern is observed in serial studies of acute and chronic states of disease the case of sarcoidosis is an example.

V DEGENERATIVE CARDIOVASCULAR DISEASES

Clinical notes

Quantitative protein estimations were performed on one hundred cases of d generative cardiovascular disease. This phrase is used to denot a group of diseases occurring in the middle aged and elderly d e to arteriosclerosis with or without hypertension. Clinical diagnoses such as coronary artery disease, cerebrovascular accident, atherosclerotic heart disease and hypertensive cardiovascular disease are included in this group The cases were distributed among three major subdivisions coronary artery diseases, cerebrovascular accidents, and nonspec ified degenerative cardiovascular diseases (Table VIII) One case of pulmonary infarction is also included.

Fifty-seven cases of clinically diagnosed coronary artery diseases were divided into three groups according to electrocardiogram findings. The first group, angina pectoris and acute coronary insufficiency comprised nineteen cases showing a myocardial ischaemia" pattern on elec trocardiography The mean serum glutamic oxaloacetic transaminase level (S G O T) was 28 units, and the mean Westergren erythrocyt sedimentation rate (E S R.) was 21 mm per hour Only two cases had leucocytosis on admission. The second group doubtful myocardial infarction, consisted of twelve cases having a myocardial damage" pattern which failed to reveal definite evidence of myocardial infarction. The mean S. G O T was 40 units and the mean E. S R. was 21 mm per hour Five cases had leucocytosis. The third group, myocardial infarction, comprised twenty-six cases in which definite evidence of myocardial infarction was obtained. The mean S. G O T was 79 units and the mean E. S R. was 35 mm per hour Sixteen cases showed leucocytosis.

Eighteen cases of cerebrovascular ac cidents were not classified because of paucity of laboratory data and the few autopsies performed. Lumbar puncture was carried out in eight cases. Six specimens were heavily blood-stained. In two cases the level of cerebrospinal fluid protein was slightly raised. The clinical diagnosis was established but the severity nature, and extent of the accident were not taken into ccount. Clinically the material ranges from mild hemiplegia to deep coma and from mild cerebral thrombosis to severe subarachnoid haemor rhage. Autopsies confirming the clinical diagnoses were performed on three of the eight fatal cases.

Twenty-four cases of cardiovascular disease associated with generalized atherosclerosis, all of which had a history of at least two years duration were further divided into two groups. There wer nine cases without marked congestive cardiac failure or with a previous history of failure controlled by drugs at the time of the test. In the second group were fifteen cases with clinical signs of congestive cardiac failure.

Results

The results set out in Tables VIII and IX may be summarized in five sections.

Table VIII Mean values of serum protein fractions cholesterol cholesterol/phospholipid ratio and hexosamine

Diagnosis	No. of cases	Mean age	A	α_1–G
Angina pectoris	19	62	3.56	0.34
Doubtful myocardial infarction	12	65	3.33	0.36
Myocardial infarction	26	68	3.33	0.37
Cerebrovascular accident	18	70	3 45	0.3b
Cardiovascular disease without congestive cardiac failure	9	68	3.25	0.31
Cardiovascular disease w th congestive cardiac failure	15	76	3 17	0.41
Pulmonary infarction	1	75	3.15	0.57

Number of cases analysed.

Table IX Distribution, in standard deviations from the normal mean, of serum protein fractions in degenerative cardiovascular d seases

Angina pectoris

Fraction	Standard deviations from normal mean																			
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	—	—	1	1	3	1	6	4	3	—	—	—	—	—	—	—	—	—	—
α_1–G	—	—	—	—	—	—	1	4	5	2	5	2	—	—	—	—	—	—	—
α –G	—	—	—	—	—	1	1	5	5	3	1	3	—	—	—	—	—	—	—
β–G	—	—	—	—	—	—	1	3	2	2	6	2	1	—	—	1	1	—	—
γ–G	—	—	—	—	—	1	4	4	4	1	—	4	1	—	—	—	—	—	—
TG	—	—	—	—	—	—	1	4	3	2	2	4	2	—	1	—	—	—	—
TP	—	—	—	—	1	2	2	3	4	6	1	—	—	—	—	—	—	—	—

Doubtful myocardial infarction

Fraction	Standard deviations from normal mean																			
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	—	—	—	2	1	4	5	—	—	—	—	—	—	—	—	—	—	—	—
α –G	—	—	—	—	—	—	—	3	2	2	1	2	1	—	—	—	—	1	—
α –G	—	—	—	—	—	—	—	5	3	1	—	2	—	1	—	—	—	—	—
β–G	—	—	—	—	—	—	—	3	3	2	1	2	1	—	—	—	—	—	—
γ–G	—	—	—	—	—	2	2	4	3	—	—	—	1	—	—	—	—	—	—
TG	—	—	—	—	—	—	1	2	3	1	2	2	1	—	—	—	—	—	—
TP	—	—	—	—	2	1	3	2	2	2		—	—	—	—	—	—	—	—

Mean value.

levels in degenerative cardiovascular diseases

α_1-G	β-G	γ-G	TG	TP	Cholesterol	Phospholipid / Cholesterol	Hexosamine
0.84	1.20	1.29	3.65	7.21	276 (10)	0.94 (9)	118 (8)
0.92	1.00	1.14	3.51	6.84	250 (5)	0.96 (4)	119 (5)
1.02	1.13	1.25	3.77	7.10	274 (5)	0.84 (1)	130 (1)
0.95	1.17	1.29	3.81	7.26	310 (12)	0.85 (12)	132 (12)
0.83	1.06	1.23	3.43	6.78	276 (5)	0.99 (5)	116 (5)
0.92	1.28	1.34	3.95	7.12	241 (5)	0.93 (5)	124 (5)
1.25	1.21	1.21	4.24	7.39	—	—	—

Table IX (cont.)

Myocardial infarction

Fraction	Standard deviations from normal mean																		
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	—	1	—	1	4	13	4	2	1	—	—	—	—	—	—	—	—	—	—
α_1-G		—	—		—	—	1	1	2	4	6	8	3	1	—	—	—	—	—
α_2-G		—	—	—	1	—	—	1	2	5	6	4	4	2	1	—	—	—	—
β-G	—		—	—	—	—	2	4	4	2	8	4	1	1	—	—	—	—	—
γ-G	—		—		—	4	4	4	5	4	2	2	—	—	—	1	—	—	—
TG		—	—		—	—	1	4	4	4	5	5	3	—	1	—	1	—	—
TP		—	—	—	1	2	6	8	6	3	—	—	—	—	—	—	—	—	—

Cerebrovascular accident

Fraction	Standard deviations from normal mean																		
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	—	1	—	2	—	6	4	3	2	—	—	—	—	—	—	—	—	—	—
α_1-G			—	—	—	—	—	1	3	7	3	2	1	—	—	1	—	—	—
α_2-G			—	—	—	—	1	1	2	2	4	5	2	—	1	—	—	—	—
β-G			—	—	—	—	1	1	3	4	4	3	2	1	—	—	—	—	—
γ-G			—	—	—	2	—	4	14	3	4	—	—	—	1	—	—	—	—
TG	—	—	—	—	—	—	—	1	4	4	5	2	2	—	1	—	1	—	—
TP	—	—	—	1	—	—	4	5	5	2	1	1	1	—	—	—	—	—	—

Mean value.

Table VIII Mean values of serum protein fractions, cholesterol, cholesterol/phospholipid ratio, and hexosamine

Diagnosis	No. of cases	Mean age	A	α_1-G
Angina pectoris	19	62	3.56	0.34
Doubtful myocardial infarction	12	65	3.53	0.36
Myocardial infarction	26	68	3.33	0.37
Cerebrovascular accident	18	70	3.45	0.36
Cardiovascular disease without congestive cardiac failure	9	68	3.25	0.31
Cardiovascular disease with congestive cardiac failure	15	76	3.17	0.41
Pulmonary infarction	1	75	3.15	0.57

Number of cases analysed.

Table IX Distribution, in standard deviations from the normal mean, of serum protein f actions in degenerative cardiovascular diseases

Angina pectoris

Frac tion	Standard deviations from normal mean																		
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	—	—	1	1	3	1	6	4	3	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	—	1	4	5	2	5	2	—	—	—	—	—	—	—
α -G	—	—	—	—	—	1	1	5	5	3	1	3	—	—	—	—	—	—	—
β-G	—	—	—	—	—	—	1	3	2	2	6	2	1	—	—	1	1	—	—
γ-G	—	—	—	—	—	1	4	4	4	1	—	4	1	—	—	—	—	—	—
TG	—	—	—	—	—	—	1	4	3	2	2	4	2	—	1	—	—	—	—
TP	—	—	—	—	1	2	2	3	4	6	1	—	—	—	—	—	—	—	—

Doubtful myocardial infarction

Frac tion	Standard deviations from normal mean																		
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	—	—	—	2	1	4	5	—	—	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	—	—	3	2	2	1	2	1	—	—	—	—	1	—
α -G	—	—	—	—	—	—	—	5	3	1	—	2	—	1	—	—	—	—	—
β-G	—	—	—	—	—	—	—	3	3	2	1	2	1	—	—	—	—	—	—
γ-G	—	—	—	—	—	2	2	4	3	—	—	—	1	—	—	—	—	—	—
TG	—	—	—		—	—	1	2	3	1	2	2	1	—	—	—	—	—	—
TP	—	—	—	—	2	1	3	2	2	2	—	—	—	—	—	—	—	—	—

Mean value.

levels in degenerative cardiovascular diseases

α-G	β-G	γ-G	TG	TP	Cholesterol	Phospholipid / Cholesterol	Hexosamine
0.84	1.20	1.28	3.63	7.21	276 (10)	0.94 (9)	118 (9)
0.92	1.09	1.14	3.51	6.84	250 (5)	0.96 (4)	119 (3)
1.01	1.13	1.25	3.77	7.10	274 (3)	0.84 (1)	130 (1)
0.93	1.17	1.29	3.81	7.26	310 (12)	0.85 (12)	132 (12)
0.83	1.05	1.23	3.45	6.78	276 (5)	0.99 (5)	116 (5)
0.92	1.28	1.34	3.95	7.12	241 (5)	0.93 (3)	124 (3)
1.25	1.21	1.21	4.24	7.39	—	—	—

Table IX (cont.)

Myocardial infarction

Fraction	Standard deviations from normal mean																		
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	–	1	–	1	4	13	4	2	1	–	–		–	–	–		–	–	–
α-G	–	–	–			–	1	1	2	4	6	8	3	1	–	–	–	–	–
α-G	–	–	–	–	1	–	–	1	2	5	+6	4	4	2	1	–	–	–	–
β-G	–	–	–	–	–	–	2	4	4	2	8	4	1	1	–	–	–	–	–
γ-G		–	–		–	4	4	4	5	4	2	2	–	–	–	1	–	–	–
TG	–		–			–	1	4	4	4	5	5	5	–	1		1	–	–
TP	–		–	–	1	2	6	8	6	5		–	–	–	–	–	–	–	–

Cerebrovascular accident

Fraction	Standard deviations from normal mean																		
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A		1	–	2	–	*6	4	3	2	–	–	–	–	–	–	–	–	–	–
α-G				–	–	–	–	1	3	7	3	2	1	–	–	1	–	–	–
α-G	–			–	–	–	1	1	2	2	4	5	2	–	1	–	–	–	–
β-G	–	–		–	–	–	1	1	3	4	4	5	2	1	–	–	–	–	–
γ-G		–		–	–	2	–	4	4	3	4	–	–	–	1	–	–	–	–
TG	–	–		–	–	–	–	1	4	4	3	2	2	–	1	–	1	–	–
TP	–	–	–	1	–	–	4	5	3	2	1	1	1	–	–	–	–	–	–

*Mean value.

Table IX (cont.)

Cardiovascular disease without congestive cardiac failure

Fraction	Standard deviations from normal mean																		
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	—	—	1	—	2	4	—	2	—	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	—	—	2	4	2	1	—	—	—	—	—	—	—	—
α_2-G	—	—	—	—	—	1	—	—	4	3	1	—	—	—	—	—	—	—	—
β-G	—	—	—	—	—	—	1	—	—	7	1	—	—	—	—	—	—	—	—
γ-G	—	—	—	—	—	1	1	1	2	2	—	2	—	—	—	—	—	—	—
TG	—	—	—	—	1	—	—	1	2	1	3	1	—	—	—	—	—	—	—
TP	—	—	—	1	—	1	3	1	1	1	1	—	—	—	—	—	—	—	—

Cardiovascular disease with congestive cardiac failure

Fraction	Standard deviations from normal mean																		
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11
A	—	—	1	2	5	3	3	1	—	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	—	—	—	—	3	5	2	1	1	1	1	—	—	1
α_2-G	—	—	—	—	—	—	—	2	4	4	2	2	1	—	—	—	—	—	—
β-G	—	—	—	—	—	—	—	1	2	4	2	2	1	—	1	—	1	1	—
γ-G	—	—	—	—	—	3	—	3	4	1	—	1	2	—	—	—	—	—	1
TG	—	—	—	—	—	—	—	2	2	2	2	2	2	1	1	1	—	—	—
TP	—	—	—	—	—	1	3	5	4	1	—	1	—	—	—	—		—	

Mean value.

(1) *Angina Pectoris* This group of patients yielded a normal pattern apart from a slightly raised β-globulin fraction

(2) *Myocardial Infarction.* The pattern was that of a slightly lowered albumin fraction and slightly raised α and total globulins The γ-globulin fraction and total proteins remain within the normal range while a high normal β-globulin fraction was encountered.

(3) *Cerebrovascular Accident.* A slightly lowered albumin fraction and slightly raised α β- and total globulins were obtained. The γ-globulins and total proteins again remained normal

(4 5) *Cardiovascular Disease with Generalized Atherosclerosis* In cases without congestive cardiac failure the pattern comprised a slight decrease in albumin All other fractions were unaltered. In cases with congestive cardiac failure the pattern was more abnormal A slight decrease in albumin together with moderately raised α_1 and β-globulins led to a slight increase in total globulins. High normal α and γ- globulins and normal total proteins were encountered.

From these analyses it is apparent that there are two distinct protein patterns irrespective of what complications may occur Patterns found in sections 2, 3 4 and 5 are similar to those observed in the early and acute phases of infection and in malignancy Such alterations have been reported by Links, Waris and Alikoski (1955) in myocardial infarction and by Sunderman and Sunderman (1957) in congestive cardiac failure. This finding may be interpreted by assuming the complications of degenerative cardiovascular disease to be characterized electrophoretically as an immediat response to tissue injury In the case of disease without congestive failure, the effect is reduced by drug control and also diminishes as the chronic phase develops.

The second pattern is an elevation of the β-globulin fraction. This fraction which is associated with the majority of the serum lipoproteins, was found to be elevated in sections 1 3 and 5 The mean value of the β-globulin fraction for the total one hundred cases was 1 16 mg per 100 ml which is a borderline abnormal value. The mean serum cholesterol concentration of forty samples was found to be 278 mg per 100 ml which is a high normal value. Earlier workers (Leinwand and Moore, 1954 Voigt and Gadermann, 1956) reported raised β-globulins in most atherosclerotic cases, but correlation with serum cholesterol and phospholipid levels failed in some individual cases. This variability is reflected in the present study in which some groups have raised mean β-globulins yet the total mean remains high normal. Therefore quantitative electrophoretic analyses can reveal a pathological excess of certain serum lipoproteins which will be manifested as an elevated β-globulin fraction. Such a finding is not pathognomonic for atherosclerosis, neither does degenerative cardiovascular disease necessarily produce increased β-globulins.

It will be convenient to refer to a pattern containing an excess concentration of one or more fractions as an augmented response to tissue injury the designation should not be pplied to patterns adequately described as immediate or delayed responses.

Clinical notes

During a six month period in 1960 quantitative electrophoretic analyses of serum proteins were performed randomly on patients directly admitted to the Royal Perth Hospital Psychiatric Unit. Clinically apparent organic diseases such as acute and chronic infections neoplastic diseases and degenerative cardiovascular diseases were excluded upon clinical and laboratory evidence. The remaining forty eight cases were referred to the Psychiatrist of the Unit for diagnosis. This procedure made it possible to classify the cases into five major groups with appropriate subdivisions (Table X) None of the patients had recently been resident in a mental institution and all were drawn from the same population as the other cases

The reasons why a group of mental diseases was included in the present survey are twofold Firstly as far as the authors are aware no such studies have been published previously in the medical literature Secondly the recent revival of the biochemical concept of certain forms of schizophrenia and of depression together with the voluminous literature

Table X Mean values of serum protein fractions in mental diseases

Disease	Number of cases	A	α_1-G	α_2-G	β-G	γ-G	TG	TP
Psychopathic personality	4	4.23	0.30	0.75	0.91	1.20	3.16	7.39
Neurosis	—	3.70	0.28	0.72	0.98	1.11	3.09	6.79
Anxiety state	3	—	—	—	—	—	—	—
Conversion hysteria	2	—	—	—	—	—	—	—
Obsessive-compulsive neurosis	1	—	—	—	—	—	—	—
Depression	20	3.56	0.32	0.80	1.01	1.14	3.27	6.83
Endogenous and reactive	—	—	—	—	—	—	—	—
Schizophrenia	—	3.69	0.35	0.89	1.01	1.14	3.39	7.08
Simple	5	—	—	—	—	—	—	—
Catatonic	1		—	—	—	—	—	—
Paranoid	2	—	—	—	—	—	—	—
Schizoaffective disorder	3	—	—	—	—	—	—	—
Organic mental state	—	3.15	0.37	0.97	1.08	1.03	3.45	6.60
Toxic confusional stat (bromide)	2	—	—	—	—	—	—	—
Atherosclerotic confusional state	1	—	—	—	—	—	—	—
Korsakow syndrom	1	—	—	—	—	—	—	—
Wernicke encephalopathy	1	—	—	—	—	—	—	—
Intermittent porphyria	1	—	—	—	—	—	—	—
Delirium tremens	1	—	—	—	—	—	—	—

Table XI Distribution, in standard deviations from the normal mean, of serum protein fractions in mental diseases

Psychopathic personality and neurosis

Fraction	Standard deviations from normal mean													
	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8
A	—	—	—	1	4	3	1	1	—	—	—	—	—	—
α -G	—	—	—	—	1	3	3	1	—	—	—	—	—	—
α_1-G	—	—	—	—	2	3	3	2	—	—	—	—	—	—
β-G	—	—	—	1	—	3	4	—	—	—	—	—	—	—
γ-G	—	—	—	—	2	3	3	2	—	—	—	—	—	—
TG	—	—	—	1	2	2	2	2	1	—	—	—	—	—
TP	—	—	—	2	2	2	2	1	1	—	—	—	—	—

Depression

Fraction	Standard deviations from normal mean													
	−6	5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8
A	1	1	—	4	8	6	—	—	—	—	—	—	—	—
α -G	—	—	—	1	2	4	8	2	2	—	1	1	—	1
α_1-G	—	—	1	—	1	5	7	4	—	1	1	—	—	—
β-G	—	—	—	1	1	4	6	3	1	1	—	1	—	—
γ-G		—	—	4	2	4	5	3	1	1	—	—	—	—
TG	—	—	—	2	3	5	3	4	3	—	2	—	—	—
TP		1	1	3	4	4	3	3	1	—	—	—	—	—

Schizophrenia

Fraction	Standard deviations from normal mean													
	−6	5	−4	3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8
A		—		2	5	3	1	—	—	—		—	—	—
α -G		—			—	2	3	*2	1	2	—	1	—	—
α -G		—		—	—	2	3	2	3	—	1	—	—	—
β-G		—	—	—	1	3	4	2	—	—	1	—	—	—
γ-G		—	—	—	2	4	4	1	—	—	—	—	—	—
TG		—	—	—	1	1	2	5	1	1	—	—	—	—
TP	—	—	—	1	1	*4	4	1	—	—	—	—	—	—

* Mean value.

which has appeared on these subjects warrants an investigation into serum protein aberrations in mental illness.

Gjessing (1938) published well controlled studies on nitrogen metabolism in periodic catatonia and suggested the possibility of a relationship between intermediary protein metabolism and schizophrenia According to Fleischhacker Lancaster and Wheeler (1959) disturbed albumin-globulin ratios were found in active idiopathic schizophrenia due mainly to increased γ-globulins Pickworth (1935) claimed a correlation between "focal infection and mental illness. Such chronic sepsis would account for elevated γ-globulin levels. However Fleischhacker Lancaster and Wheeler (1959) failed to confirm such a correlation.

Results

The results detailed in Tables X and XI fail to show significant disturbances in the serum protein fractions. Organic mental states however produced the characteristic Immediate response pattern to tissue injury Moderately lowered albumin and slightly raised α-globulin fractions were obtained. The remainder of the pattern was normal. It is noteworthy that while the psychopathic, neurotic, and depressive groups provide normal mean globulin levels the schizophrenic group reveals a low normal albumin and high normal α globulin fractions. A detailed survey with accurate subdivisions is necessary to provide a more complete state of knowledge on a possible protein abnormality in mental disease

Clinical notes

Eighteen cases of bronchial asthma were divided into two groups: fifteen cases were analysed during asthmatic attack, and the other three were undergoing steroid treatment. The mean age of the untreated was 35 years. Cases were selected after clinical diagnosis and gave a long history of recurrent attacks. Some of the younger patients had suffered from asthma since early childhood. The infectious element played a large part in the precipitation of these attacks. Seven cases showed leucocytosis and in six cases a history of an association of upper respiratory tract infection with the occurrence of asthmatic attack was elicited. The three steroid treated cases had been receiving prednisone for a considerable time prior to analysis. Two were having an attack at the time, and the other was in a quiescent phase, when blood was collected.

Results

From the results in Tables XII and XIII it appears that the serum protein pattern consists of a low normal albumin, high normal α_1- and γ-globulins and slight elevations in α_2- β- and total globulins. The total protein level remains within the normal range. The steroid-treated asthmatics showed a normal protein pattern, with a low normal albumin and high normal α_2-globulin fraction. The total proteins were in the low normal range.

An earlier electrophoretic report of thirteen cases of bronchial asthma (Jencks, Smith and Durrum, 1956) described decreases in albumin and increases in all globulin fractions. In the present survey only three cases showed raised γ-globulins but elevation of the β-globulins was noted in seven cases. The nature and origin of this increment are puzzling. Since the mean age of the group is only 35 years and the phospholipid cholesterol ratio is 1.02, it is improbable that it derives from β_1-lipoprotein as in the atherosclerotic cases. The other possibility is that the raised β-globulins arise from the recently isolated β_2A-globulin (Heremans, Heremans and Schultze, 1959) and fast moving antibodies. If this is so, then the observed elevation implies a delayed reaction to tissue necrosis similar to the findings in viral infection.

The raised α_1- and high normal α_2-globulins probably represent the same

Table XII. Mean values of serum protein fractions in bronchial asthma

Group	Number of cases	A	α_1-G	α_2-G	β-G	γ-G	TG	TP
Untreated	15	3.58	0.30	0.93	1.24	1.32	3.87	7.45
Steroid-treated	3	3.47	0.33	0.75	0.57	1.02	3.04	6.51

Table XIII Distribution, in standard deviations from the normal mean of serum proteins in untreated bronchial asthma

Fraction	Standard deviations from normal mean													
	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9
A	1	—	3	8	2	1	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	1	3	3	2	3	1	—	—	1	1
α -G	—	—	—	—	2	4	1	4	4	—	—	—	—	—
β-G	—	—	—	—	1	1	6	2	2	1	—	1	—	1
γ-G	—	—	1	—	2	4	5	2	1	—	—	—	—	—
TG	—	—	—	—	1	2	3	4	3	1	—	—	1	—
TP	—	—	—	2	4	4	3	1	1	—	—	—	—	—

Mean value.

response to that observed earlier as an immediate response to injury Therefore bronchial asthma produces a mixed type of disturbance on the serum proteins The underlying delayed response is concomitant with the superimposed immediate response to tissue destruction. Such a hypothesis accords with the chronic clinical state of bronchial asthma with its periodic exacerbation due to various traumatic stimuli such as infection allergy or emotional state.

Thirteen cases of clinically diagnosed skin diseases were grouped as arranged in Table XIV Significant abnormalities in the serum protein patterns occurred in two groups exfoliative dermatitis and pemphigus vulgaris.

Results

In exfoliative dermatitis there is a slight decrease in albumin, a slight increase in th γ-globulins, a slight increase in β-globulins, and marked increases in the α and γ-globulins. An increased γ-globulin level persisted in the case of pemphigus vulgaris.

Apart from the slightly lowered albumin fraction observed in neurodermatitis, no variations outside the normal range were encountered in any fractions in allergic dermatitis, dermatitis herpetiformis, or psoriasis. Sunderman and Sunderman (1957) reported a protein pattern similar to that in acute infection or neoplastic disease in six cases of psoriasis.

It is concluded from the present series that exfoliative dermatitis gives rise to concurrent type of electrophoretic pattern in which an immediate and a delayed response occur simultaneously Such a behaviour has already been observed in bronchial asthma. On the other hand, protein disturbances in pemphigus vulgaris ar characterized by the delayed reaction pattern seen earlier in chronic infection. In the other groups, where low and high normal figures indicate a dysproteinaemic tendency no definite conclusions can be drawn by virtue of the insignificant alterations and small numbers of the cases vailable.

Table XIV Mean values of serum protein fractions i skin diseases

Disease	Number of cases	A	α-G	α_2-G	β-G	γ-G	TG	TP
Allergic dermatitis (untreated)	3	3.76	0.31	0.82	0.98	1.35	3.46	7.22
Allergic dermatitis (steroid-treated)	1	3.44	0.32	0.62	0.95	0.97	2.86	6.30
Neurodermatitis	1	3.11	0.30	0.77	1.01	1.11	3.19	6.30
Dermatitis herpetiformis	1	3.26	0.32	0.79	0.93	1.22	3.28	6.54
Exfoliative dermatitis	3	3.23	0.41	1.03	1.05	1.77	4.26	7.49
Psoriasis	3	3.79	0.31	0.86	1.13	1.22	3.52	7.31
Pemphigus vulgaris	1	3.73	0.33	0.79	1.13	1.70	3.93	7.70

Table XIII Distribution, in standard deviations from the normal mean, of serum proteins in untreated bronchial asthma

Fraction	Standard deviations from normal mean													
	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9
A	1	—	3	8	2	1	—	—	—	—	—	—	—	—
α_1–G	—	—	—	—	1	9	3	2	3	1	—	—	1	1
α_2–G	—	—	—	—	2	4	1	4	4	—	—	—	—	—
β–G	—	—	—	—	1	1	6	2	2	1	—	1	—	1
γ–G	—	—	1	—	2	4	5	2	1	—	—	—	—	—
TG	—	—	—	—	1	2	3	4	3	1	—	—	1	—
TP	—	—	—	2	4	4	3	1	1	—	—	—	—	—

Mean value.

response to that observed earlier as an immediate response to injury Therefore bronchial asthma produces a mixed type of disturbance on the serum proteins. The underlying delayed response is concomitant with the superimposed immediate response to tissue destruction. Such a hypothesis accords with the chronic clinical state of bronchial asthma with its periodic exacerbation due to various traumatic stimuli such as infection allergy or emotional state.

Table XV Mean values of serum protein fractions in haematological diseases

Disease	Number of cases	A	α_1-G	α_2-G	β-G	γ-G	TG	TP
Myeloproliferative disorders								
Chronic myeloid leukaemia	9	3.52	0.36	0.82	0.99	1.08	3.25	6.77
Acute myeloid leukaemia	3	2.94	0.43	0.82	1.06	1.07	3.52	6.46
Myelofibrosis	7	3.38	0.36	0.80	0.95	1.03	3.14	6.52
Polycythaemia vera	6	3.25	0.38	0.84	1.16	1.25	3.63	6.89
Erythroleukaemia	2	3.32	0.32	0.49	0.91	1.32	3.04	6.35
Lymphomas								
Follicular lymphoma	5	3.68	0.31	0.73	0.86	0.89	2.79	6.48
Lymphosarcoma	4	2.90	0.48	0.91	1.22	1.28	3.88	6.78
Reticulum cell sarcoma	2	3.20	0.37	0.74	0.83	1.37	3.30	6.50
Hodgkin disease	3	2.98	0.36	1.05	1.29	1.80	4.50	7.48
Chronic lymphocytic leukaemia	13	3.62	0.34	0.77	0.88	0.77	2.76	6.38
Mycosis fungoides	2	3.18	0.34	0.81	1.11	1.91	4.17	7.35
Pernicious anaemia (untreated)	4	3.72	0.30	0.54	0.75	0.85	2.43	6.15
Iron-deficiency anaemia	5	3.48	0.36	0.84	1.16	1.18	3.56	7.04
Haemolytic anaemia								
Auto-immune anaemia	6	3.98	0.32	0.69	0.92	1.78	3.71	7.69
Drug-induced anaemia	1	4.48	0.31	0.50	0.78	0.27	1.86	6.34
Purpura hyperglobulinaemica	2	3.32	0.31	0.69	1.21	3.46	5.67	8.98
Haemophilia	1	4.28	0.32	0.54	1.01	0.92	2.79	7.07
Myeloma								
β-paraproteinaemia	7	2.24	0.31	0.76	6.48	0.39	7.95	10.19
M-paraproteinaemia	1	2.94	0.30	0.64	0.78	0.23	6.31	9.25
γ-paraproteinaemia	12	2.50	0.35	0.68	0.92	4.64	6.79	9.29
Diffuse β-globulinaemia	2	3.76	0.38	0.90	1.41	0.70	3.58	7.14
Diffuse γ-globulinaemia	2	2.25	0.33	0.78	1.22	3.38	5.73	7.96
Macroglobulinaemia	8	2.34	0.39	0.89	0.81	3.43	5.54	7.88
Idiopathic paraproteinaemia								
M-paraproteinaemia	2	—		—	—	—	—	—
γ-paraproteinaemia	5	—	—	—	—	—	—	—

Value of M-globulin, between β- and γ-globulin, is 4.36.

This group was considered too heterogeneous to warrant calculation of mean values.

treated and one had relapsed. Their serum iron levels ranged from 10 to 61 μg per 100 ml with a mean of 33 μg per 100 ml. The haemoglobin values varied from 6.4 to 12.4 g % with a mean of 9.3 g %.

Seven cases of acquired haemolytic anaemia consisted of six of the auto-immune and one of the drug-induced type. In the former the direct Coombs' test was strongly positive in all cases. In one case the γ-globulin neutralization test indicated a warm type of antibody. This patient had the highest γ-globulin of the group (3.07). In two cases no inhibition in the presence of γ-globulin was found; this is suggestive of a cold type of antibody. Drug-induced haemolytic anaemia showed a different picture resembling haemolytic anaemia associated with lymphoma.

IX HAEMATOLOGICAL DISEASES

Clinical notes

One hundred and fourteen cases of haematological diseases were classified into nine major subdivisions (Table XV). Of the myeloproliferative disorders, twelve cases of myeloid leukaemia were confirmed by bone marrow biopsy: nine were of the chronic type and three were acute. Infection was present in two chronic and two acute cases. Anaemia ranged from haemoglobin levels of 7.0 gm% to 13.6 gm% with a mean value of 10.1 gm%.

Five of the seven myelofibrotic cases had been diagnosed for some years, the remainder being only recently diagnosed. All seven cases revealed varying degrees of anaemia ranging from 3.9 g% to 11.4 g% with a mean value of 8.9 g%. No clinically apparent infection could be detected in these patients at the time of analysis.

Of six cases of polycythaemia vera, four were recently diagnosed and two were of a few years standing. Although the latter had received radioactive phosphorus treatment, both showed marked disease activity at the time of the test. One of the recently diagnosed cases presented with gangrene of the toes: this is perhaps responsible for the highly elevated α-globulin fractions on electrophoresis. In another case hepatic cirrhosis complicated the polycythaemia, producing a high γ-globulin level on analysis. In the remainder of the cases no complication was observed.

In erythroleukaemia electrophoresis was performed on two chronic cases of a few years duration. These patients have been frequently transfused because of refractory anaemia. Haemoglobin levels of the patients were 7.5 g% and 7.6 g%.

With the exceptions of lymphatic leukaemia and mycosis fungoides, clinical diagnosis of the lymphoma cases was confirmed by lymph node biopsy. Haemolytic anaemia was absent. Of three cases whose lymph node biopsy showed the characteristic picture of Hodgkin's disease, one was advanced with pneumonic infiltration and the patient died a few months after analysis. The others were recently diagnosed.

Of thirteen cases of lymphatic leukaemia one half was recently diagnosed, the remainder having a history of several years. The only case of lymphocytic leukaemia showing high α-globulin levels was one in which carcinoma of the rectosigmoid colon complicated the clinical picture. However, even in this case the commonly observed low γ-globulin fraction in chronic lymphatic leukaemia was present (0.39).

Four cases of recently diagnosed Addisonian anaemia were examined. The haemoglobin levels ranged from 3.4 g% to 10.5 g% with a mean of 6.9 g%. Bone marrow biopsy indicated megaloblastic erythropoiesis and histamine-fast achlorhydria was present. All cases showed good reticulocyte response to vitamin B_1 administration. In one of them the clinical picture of subacute combined degeneration of the spinal cord was present.

Of five patients with uncomplicated iron-deficiency anaemia, four were un

Table XVI Distribution, in standard deviations from the normal mean, of serum proteins in haematological diseases

Myeloproliferative disorders

Fraction	Standard deviations from normal mean																		
	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12
A		2	4	5	3	6	5	2	—		—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	1	2	3	8	5	5	—	—	—	—	2	—	—	1
α_2-G			—	1	—	4	8	5	3	3	2	—	1	—	—	—	—	—	—
β-G	—	—	—	—	1	5	5	*6	4	3	—	—	2	1	—	—	—	—	—
γ-G	—	—	—	—	5	4	*6	6	3	1	2	—	—	—	—	—	—	—	—
TG			—		3	2	4	5	5	5	2	1	—	—	—	—	—	—	—
TP	—	—	—	5	2	6	7	6	1	—	—	—	—	—		—	—	—	—

Lymphomas

Fraction	Standard deviations from normal mean																		
	−7	−6	5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12
A	1	2	2	4	6	4	6	4	—		—	—	—	—	—		—	—	—
α -G			—	—		—	5	8	6	4	4	1		—		—	—	1	—
α -G	—	—	—		3	2	7	10	1	2	3	1	—	—	—	—		—	—
β-G	—	—	1	—	2	4	6	7	4	3		1		—	1	—	—	—	—
γ-G			2	3	3	6	5	3	—	2	3	1	1	—	—	—	—	—	—
TG		—	—	1	2	11	5	1	2	1	1	4	—	1	—	—	—	—	—
TP	—	1	2	2	6	7	4	2	4	1	—	—		—	—		—	—	—

* Mean value.

of hemoglobin per 100 ml, whereas the serum of a patient with eyrthroleukaemia bound only 10 mg per 100 ml. Owing to the direct relation operating between haemoglobin and haptoglobin, it is natural to expect (as first pointed out by Nyman, Gydell and Nosslin 1959) that ineffective erythropoiesis will incur a subnormal haptoglobin level. A lowered α_2-globulin concentration, normally one quarter of which is haptoglobin (Nyman, 1959) can therefore be expected in erythroleukaemia in which excessive red cell destruction also occurs. Therefore the protein pattern in the myeloproliferative disorders is characterized by an immediate response to tissue injury coupled with a depletion pattern in some cases, due to hypohaptoglobinaemia arising either from haemolysis or increased intramedullary haemoglobin turnover.

Depletion patterns, which may be defined as the electrophoretic effect of the reduction or absence of one or more constituents within one or more protein fractions, were also observed in follicular lymphoma and chronic lymphocytic leukaemia where low normal albumin levels

The next two subdivisions consisted of two cases of the rare disorder described by Waldenström benign hyperglobulinaemic purpura and one case of haemophilia, respectively

Twenty four cases of clinically diagnosed myeloma were grouped according to their electrophoretic appearance. Four failed to show an abnormal discrete band (paraprotein) but of these, two had raised diffuse β-globulin and two raised γ-globulin fractions Seven myeloma patients presented with a few months history of increasing backache, three with pathological fractures, three with anaemia and pneumonia three with generalized lymphadenopathy and hepato-splenomegaly one with a four month history of increasing paraplegia, one with chronic nephritis, one with increasing lump in the right sternoclavicular region and one with a ten week history of progressive gangrene of the feet. In four cases no history was available. Ten cases showed X ray evidence of osteolytic deposits or advanced osteoporosis Bone marrow biopsy revealed definite evidence of myeloma in fourteen cases In six cases the bone marrow did not show characteristic pathological changes and in four cases no records were available Bence Jones proteinuria was detected in seven cases. Cryoglobulins were found in two sera The final diagnosis of myeloma was obtained in four cases only from autopsy findings

Of eight macroglobulinaemic patients, six presented with a long history of refractory anaemia, and lymphadenopathy was found in three A protracted history of recurrent infection was elicited in three cases and a further case was discovered accidentally following an elective haemorrhoidectomy The patient developed pneumonia and died shortly afterwards autopsy revealed a purulent leptomeningitis. Characteristic small type lymphocytic infiltration of the bone marrow was found in five cases, but not in the other three. High E S R. figures were obtained in all and anemia was present in all except one, of the cases. Typical elevation of S 19 globulins provided ultracentrifugal confirmation of macroglobulinaemia in every case.

Results

From the results in Tables XV and XVI it can be seen that the electrophoretic patterns in myeloid leukaemia and myelofibrosis are similar being characterized by a slight albumin decrease and a slight increase in the α -globulin fraction The remaining proteins are within the normal range. Neely and Neill (1956) report similar changes in chronic myeloid leukaemia however together with Sunderman and Sunderman (1957) they also observed an elevation of the γ-globulins. None of the present twelve cases revealed this alteration, and these observations are in agreement with a recent survey (Ogryzlo Maclachlan Dauphinee and Fletcher 1959) In polycythaemia vera the pattern is essentially the same as in the previous two diseases but high normal to slight increases in β-globulins were noted

In erythroleukaemia a normal electrophoretic pattern was encountered apart from a slight decrease in albumin and α_2-globulin fractions. An attempt was made to correlate the finding of a lowered α -globulin concentration with hypohaptoglobinaemia (Fig 1) Using the haptoglobin saturation method of Nyman (1959) who showed that the haemoglobin binding capacity of serum is equal to its free haptoglobin content a normal control serum was found to bind 60 mg

Table XVI Distribution, i standard deviations from the normal mean, of serum proteins in haematological diseases

Myeloproliferative disorders

Fraction	Standard deviations from normal mean																		
	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12
A	–	2	4	5	3	6	5	2	–	–	–	–	–	–	–	–	–	–	–
α-G	–	–	–	–	–	1	2	3	8	5	5	–	–	–	–	2	–	–	1
α_2-G	–	–	–	1	–	4	8	3	3	3	2	–	1	–	–	–	–	–	–
β-G	–	–	–	–	1	3	3	*6	4	3	–	–	2	1	–	–	–	–	–
γ-G	–	–	–	–	3	4	6	6	3	1	2	–	–	–	–	–	–	–	–
TG	–	–	–	–	3	2	4	3	5	5	2	1	–	–		–	–	–	–
TP	–	–	–	5	2	6	7	6	1	–	–	–	–	–		–	–	–	–

Lymphomas

Fraction	Standard deviations from normal mean																		
	−7	6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12
A	1	2	2	4	6	4	6	4	–	–	–	–			–	–	–	–	–
α-G			–	–	–	–	5	8	6	4	4	1		–	–	–	–	1	–
α-G	–	–			3	2	7	10	1	2	3	1	–	–	–	–	–	–	–
β-G			1		2	4	6	7	4	3		1			1	–	–	–	–
γ-G			2	3	3	6	5	3	–	2	3	1	1	–	–	–	–	–	–
TG		–		1	2	11	5	1	2	1	1	4		1	–	–	–	–	–
TP	–	1	2	2	6	7	4	2	4	1		–	–	–	–	–	–	–	–

Mean value.

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Of eight macroglobulinaemic patients, six presented with a long history of re fractory anaemia and lymphadenopathy was found in three. A protracted history of recurrent infection was elicited in three cases and a further case was discovered accidentally following an elective haemorrhoidectomy The patient de veloped pneumonia and died shortly afterwards autopsy revealed a purulent leptomeningitis. Characteristic small type lymphocytic infiltration of the bone mar row was found in five cases, but not in the other three. High E S R. figures were obtained in all and anemia was present in all except one, of the cases. Typical elevation of S 19 globulins provided ultracentrifugal confirmation of mac roglobulinaemia in every case.

Results

From the results in Tables XV and XVI it can be seen that the electrophoretic patterns in myeloid leukaemia and myelofibrosis are similar being characterized by a slight albumin decrease and a slight increase in the α -globulin fraction. The remaining proteins are within the normal range. Neely and Neill (1956) report similar changes in chronic myeloid leukaemia however together with Sunder man and Sunderman (1957) they also observed an elevation of the γ-globulins. None of the present twelve cases revealed this alteration, and these observations are in agreement with a recent survey (Og ryzlo Maclachlan, Dauphinee and Flet cher 1959) In polycythaemia vera the pattern is essentially the same as in the previous two diseases but high normal to slight increases in β-globulins were noted

In erythroleukaemia a normal electrophoretic pattern was encountered apart from a slight decrease in albumin and α_1-globulin fractions. An attempt was made to correlate the finding of a lowered α -globulin concentration with hypohaptoglobinaemia (Fig 1) Using the haptoglobin-saturation method of Nyman (1959) who showed that the haemoglobin-binding capacity of serum is equal to its free haptoglobin content, a normal control serum was found to bind 60 mg

ings were recorded by Arends, Coonrad and Rundes, 1954.

In untreated Addisonian anaemia, slight decreases were observed in α_1- and total globulins. It is thus purely a depletion pattern. N significant deviation from the normal pattern was noted in iron-deficiency anaemia. The only abnormality in the auto-immune type of haemolytic anaemia is a moderately raised γ-globulin fraction. The low normal to slightly lowered α_2-globulins in all cases of pernicious and haemolytic anaemia correlates well with the usual depletion of serum haptoglobins in these disorders (Chevallier and Wolpé, 1945)

It has been stated that the incidence of hypogammaglobulinaemia in diseases of the reticuloendothelial system is 22 %, whereas all other diseased patients show an incidence of less than 1 % if the nephrotic syndrome is excluded (Wall, 1958) All forms of acute leukaemia, especially acute lymphocytic leukaemia, may have lowered γ-globulin levels In chronic leukaemia the incidence is much higher in the lymphatic than the myelogenous type, while more cases are observed in lymphosarcoma than in reticulum cell sarcoma (Wall, 1958) Jim (1957) observed subnormal levels in one third of his cases of chronic lymphatic leukaemia.

In the present study the occurrence and incidence of hypogammaglobulinaemia in the absence of paraproteins were as follows acute myeloid leukaemia 1 of 2 cases, chronic myeloid leukaemia 1 of 10 myelofibrosis 3 of 7 follicular lymphoma 1 of 5 chronic lymphatic leukaemia 7 of 13 pernicious anaemia 2 of 4 and in the single case of drug-induced haemolytic anaemia. The occurrence of low levels in follicular lymphoma and their absence in lymphosarcoma and reticulum cell sarcoma may conceivably be due to compensation by auto-immunity of antibody suppression arising from leucocytic proliferation.

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In the rarer disorders, slightly lowered albumin, slightly raised β-globulins and markedly high γ-globulin levels were found in purpura hyperglobulinaemica. Here the generalized cirrhotic-like increase over the whole antibody range is suggestive of a β_2A-globulin increment. The haemophiliac yielded a normal pattern apart from a slightly lowered α_2-globulin fraction.

In the myeloma cases displaying a paraprotein in the electrophoretic pattern, albumin and γ-globulin levels were invariably low That the antibody levels are low in the γ-paraprotein cases appears highly probable in the light of such patients susceptibility to infection and the experimentally supported hypothesis that the paraproteins are not globulins normally present in serum but abnormal products of a deranged protein synthesis (Putnam, 1959) The β-paraprotein concentrations were on the average higher than their γ counterparts.

In the four cases devoid of discrete paraproteins, the two cases of elevated γ-globulin fractions were coupled with severely depleted albumin levels and somewhat raised β-globulins. The other two cases resembled β- and M-paraproteins in having elevated β-fractions associated with low γ-globulins the albumin levels were not nearly so low. Dye uptake studies on discrete spiked electrophoretic bands lead to the conclusions that although some paraproteins have the same binding capacity as normal γ-globulin, an abnormal dye-binding capacity is invariably associated with abnormal proteins (Brackenridge, 1960 d) Ogryzlo, Maclachlan, Dauphinee and

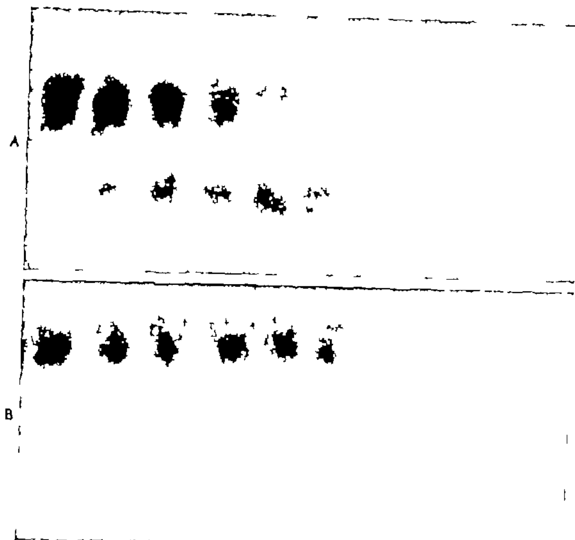


Fig 1 Saturation of th haptogl bin-haemoglobin complex (fast mov ng band, below) with haemoglobin (sl w moving band, above) in amounts added from the right: 10, 30 50 70, 90 110, 130 150 170 and 190 mg per 100 ml. A shows haptoglobin in normal serum binds about 60 mg of haemoglobin, while B shows only bout 10 mg are bound in a serum from a case of erythro leukaemia.

were associated with low normal or slightly decreased γ-globulins. These find ings are in agreement with earlier workers (Brown Read Wiseman and France 1948 Sunderman and Sunderman 1957) In contrast lymphosarcoma, reticulum cell sarcoma, and Hodgkin s disease show an entirely different trend. Here the hypoalbuminaemia together with generalized normoglobulinaemia to hyperglobulinaemia indicate a gradual change from the immediate to the delayed response pat tern, both types operating in Hodgkin s disease. Similar findings have been observed by Rottino Suchoff and Stern (1948) Jencks, Smith and Durrum (1956) and Sunderman and Sunderman (1957) in Hodgkin s disease, and by Neely and Neill (1956) in reticulum cell sarcoma. In mycosis fungoides a slightly de pleted albumin fraction and an elevated γ-globulin level were found similar find

Case 2. A. N. is 72-year-old Yugoslav man who was admitted with one-week history of nausea, vomiting, diarrhoea, and epigastric pain related to meals. Barium meal revealed an increase in the size of the gastric ulcer which was noted one year before. Electrocardiography suggested probable anterior myocardial damage. A long history of sensitivity to cold especially in hands and feet was given. There was no evidence of purpura, ulceration or gangrene of the extremities. Haematological findings were haemoglobin 15.8 g %, white cell count 4,200 per mm³ E.S.R. 19 mm per hour. The electrophoretic analysis showed an M-paraprotein band and slightly lowered γ-globulin level. Refrigeration resulted in the precipitation at 4° C of paraprotein from the serum. The patient was treated conservatively and made satisfactory progress. A repeat analysis performed in the summer six months later showed no trace of paraprotein, and no cryoglobulin could be isolated from the serum.

Bohrod (1957) has also reported the disappearance of cryoglobulin, and similar phenomenon has been described in the case of macroglobulin in the serum of patient after four years (Ferriman and Anderson, 1956; Anderson and Ferriman, 1960).

Case 3. D. A. is 67-year-old white female who was transferred from the mental hospital where she was admitted recently with the diagnosis of paranoid schizophrenia. The reason for transfer was to stabilize her diabetic state. On examination she was found to have lump in the left breast. It was fixed to the skin but not to deeper structures and there were no palpable lymph nodes in the axillae. According to surgical opinion, it was scirrhous carcinoma of the breast. The patient also had an old keratitis of the right eye of very low activity. Haematological data were haemoglobin 13.5 g %, white cell count 9,500 per mm³. E. S. R. 45 mm per hour. Sternal puncture was not performed. The Wassermann reaction was once positive and twice negative in three repeated examinations. A skeletal X-ray survey failed to reveal any bony abnormality. Liver function tests were normal. The patient diabetes was stabilized and she was transferred to the mental hospital on Diabenase. Electrophoresis showed moderate discrete γ-paraprotein associated with low albumin and slightly raised α_2-globulin fraction.

Case 4. F. L. is 65-year-old white male who was admitted with three-week history of epigastric pain and an exacerbation of his chronic bronchitis. On examination he was tender in the right hypochondrium and his liver was palpable 3 cm below the right costal margin. Four months previously the patient was admitted with right lower lobe pneumonia and it was discovered that he had fractured 6, 7, 8, and 9th ribs. No reason for this was offered, so it was assumed due to trauma. The haemoglobin level was 17.3 g %, white cell count 12,400 per mm³ E. S. R. 31 mm per hour, neutrophils 94 % metamyelocytes 1 %, lymphocytes 4 % and monocytes 1 %. Bone marrow biopsy revealed no diagnostic features. An X-ray survey of the skeletal system showed nothing abnormal. No Bence Jones proteinuria was found on repeated examinations. The barium meal was normal. Electrophoresis showed a γ-paraprotein of high concentration superimposed on typical acute infection pattern. One week later the liver function tests returned to normal, and three weeks later intravenous cholecystography failed to reveal any abnormality of gall bladder or bile duct. The patient recovered and was discharged.

Case 5. H. J. is an 86-year-old white male who was admitted with chronic retention of urine with overflow. The patient gave history of several years of dysuria suggesting prostatomegaly. His haemoglobin level was 6.0 g %, haematocrit 20 %, leucocyte count 8,000, and E. S. R. 73 mm per hour. The blood picture showed neutrophils 53 %, lymphocytes 34 %, monocytes 9 %, eosinophils 3 %, basophils 1 with occasional myelocytes and increased rouleaux formation. Skeletal survey revealed extensive Paget' disease of the pelvic bone. The bone marrow was not examined, and lungs appeared clear. The patient underwent prostatectomy from which he recovered satisfactorily. The pathology report revealed an adenoma of the prostate gland. Electrophoresis showed γ-paraprotein of high intensity with lowered amount of albumin and levels of the intermediate globulins which tended to be low.

Table XVII Mean values of serum protein fractions in seven patients with idiopathic paraproteinaemia

Case Number	Sex	Age	A	α_1-G	α_2-G	β-G	M-G	γ-G	TG	TP
1	M	57	3.52	0.37	0.91	1.08	2.16	0.48	5.03	8.55
2	M	72	3.25	0.29	0.72	1.00	0.80	0.76	3.57	6.82
3	F	67	2.95	0.26	1.02	1.05	—	1.27	3.60	6.55
4	M	65	2.44	0.56	1.17	0.80	—	1.81	4.34	6.78
5	M	86	3.04	0.30	0.69	0.62	—	3.67	5.28	8.32
6	M	70	3.39	0.28	0.76	0.94	—	2.82	4.80	8.19
7	M	71	2.74	0.48	1.09	0.97	—	2.21	4.75	7.49

Paraprotein.

Fletcher (1959) observed that 10 % of their myeloma cases yielded no para protein band on serum electrophoresis but that all such cases produced an abnormal band on urinary electrophoresis In the present study only one of the four cases (a Bence Jones positive case) yielded a generalized hyperglobulinaemic type of pattern on urinary electrophoretic analysis All myeloma proteins migrated on starch gel

All eight macroglobulinaemic sera revealed typical elevated γ-paraprotein bands when analyzed the mean pattern displayed a very low albumin, otherwise no other abnormality was present. All paraproteins failed to migrate on starch gel, and none were cryoglobulins. Electrophoretically no differences were seen to exist between γ-paraprotein myeloma and macroglobulinaemia Starch gel electrophoresis and ultracentrifugation are therefore necessary to confirm macroglobulinaemia

In seven instances, paraproteins were found in sera of patients with diseases which defied classification as myeloma, macroglobulinaemia or any other haematological disorder All seven abnormal proteins migrated on starch gel and none were macroglobulins of the 19 S type as judged ultracentrifugally An increasing stream of publications has appeared from authors who have recognized the importance of documenting case histories of patients exhibiting anomalous or idiopathic paraproteinaemia (Azar Hill and Osserman 1957 Bohrod, 1957 Osserman, 1958 1959 Ogryzlo Maclachlan, Dauphinee and Fletcher 1959 Owen, Pitney and O Dea, 1959) Following are the case histories electrophoretic results are shown in Table XVII

Case I M. C. is a 57 year-old white male who was admitted with sudden severe retrosternal pain. Electrocardiography showed evidence of coronary occlusion Anticoagulant therapy with heparin and dindevan was commenced. It was discontinued 24 hours after admission because of a small haematemesis. Haematological data were haemoglobin 16 7 g % packed cell volum 50 white cell count 18,000 per mm³ neutrophils 83 lymphocytes 8 % monocytes 8 % metamyelocytes 1 % E. S R 21 mm per hour His chest X-ray was normal. Skull and other long bones were normal. Bone marrow biopsy was not performed The electrophoretic pattern showed a quite intense discrete M paraprotein associated with a γ-globulin deficiency The patient made a satisfactory recovery however electrophoresis carried out two months later still showed the presence of an M-paraprotein. It is evident that myeloma has not been completely excluded.

X GASTROINTESTINAL DISEASES

Clinical notes

Forty-four cases of gastrointestinal diseases were subdivided as shown in Table XVIII

Of eleven cases of chronic peptic ulcer diagnosed clinically and supported by barium meal evidence of ulcer crater two presented with haematemesis and three with a few days' history of melaena motion. The remaining cases presented the characteristic history of epigastric pain related to meals.

The cases of ulcerative colitis in various stages of progression were of at least one year' standing with the exception of one with a three-month history of diarrhoea with blood and mucus. One case gave a history of fifteen years' duration. Three of the chronic cases had been treated with steroids at some stage of the illness, but none was receiving steroids at the time of analysis. All presented with acute exacerbation of ulcerative colitis and two patients had to have total colectomy performed.

One case of Crohn's disease, proved at an appendicectomy operation, was supported by barium meal and follow-through examination.

Four of seven cases of malabsorption syndrome of varying severity presented with abdominal discomfort and related symptoms. Three of the seven had a previous partial gastrectomy One patient presented with abdominal symptoms and symptoms of peripheral neuritis, one with the clinical picture of pellagra and megaloblastic anaemia, and one with tabes dorsalis. In four cases barium meal and follow-through examination suggested a malabsorption pattern. The xylose absorption test results ranged from 1.5 to 4.2 g per 5 hours, with a mean of 2.5 g per 5 hours. Serum carotene levels of 14 to 46 μg per 100 ml with a mean 27 μg per 100 ml were obtained. Faecal fat studies showed characteristic abnormalities.

Table XVIII Mean values of serum protein fractions in gastrointestinal diseases

Disease	Number of cases	A	α_1-G	α_2-G	β-G	γ-G	TG	TP
Chronic peptic ulcer	11	3.50	0.37	0.81	1.12	1.09	3.39	6.89
Early ulcerative colitis	1	4.11	0.25	0.57	0.98	0.87	2.67	6.78
Chronic ulcerative colitis	5	2.47	0.53	0.88	0.93	1.75	3.91	6.38
Crohn disease	1	3.71	0.34	0.86	0.66	1.16	3.02	6.73
Malabsorption syndrome	7	2.72	0.53	0.78	0.94	1.23	3.29	6.01
Pancreatitis	4	3.40	0.37	1.08	1.13	1.36	3.93	7.33
Cholelithiasis with acute cholecystitis	9	3.22	0.43	1.05	1.14	1.21	3.82	7.04
Cholecystitis without cholelithiasis	2	2.69	0.46	0.99	1.16	1.17	3.77	6.46
Cholelithiasis without acute cholecystitis	4	3.56	0.33	0.81	1.17	1.04	3.35	6.91

Case 6. J H. is a 70-year-old white male who presented at an orthopaedic clinic because of an episode of back pain ten weeks previously which later settled in the right groin and radiated to the right knee. The patient had been treated for back pain ten years previously The haematological details were haemoglobin 13 7 g % haematocrit 42 % leucocyte count 7 200 per mm E S. R. 41 mm per hour neutrophils 65 % lymphocytes 25 % monocytes 8 % eosinophils 2 % Skeletal survey revealed that appearance of the pelvic bone and knees was normal. However the lumbar vertebrae showed extensive osteoporosis and the anterior part of the L_1 vertebra was moderately wedged. Lung X ray showed an old calcified lesion in the right upper lobe. The response to a glucose tolerance test indicated that the patient was a diabetic. Normal values for serum alkaline phosphatase, calcium and inorganic phosphate were obtained. Bone marrow b opsy was not performed The patient was given physiotherapy and hormone therapy commenced Electrophoresis revealed a large γ-paraprotein and a lowered albumin content.

Case 7 F B. is a 71-year-old white male who presented with a three-day history of fever cough, and chest pain. He also complained of long-standing dysuria which was diagnosed at the time as prostatitis. The patient was drowsy and dehydrated on admission, when a tentative diagnosis of acute or chronic bronchitis and chronic retention of urine was made. Haematological findings were haemoglobin 14.9 g % haematocrit 44 % leucocyte count 6,200 showing polymorphonuclear leucocytosis, and E. S R. 60 mm per hour Increased rouleaux formation was noted. Bone marrow biopsy revealed no diagnostic features, and a skeletal survey failed to detect any abnormality The patient was treated with chloromycetin and penicillin and his condition eventually improved. Paraproteinaemia persisted as judged by repeated electrophoretic analysis.

Reviewing these histories it will be seen that the patients were predominantly males, the mean age was 70 and that the variety of presenting symptoms was wide In all cases the E. S R. level correlated with the paraprotein concentration. Arising from the present study it is concluded that

(1) Paraproteins are always found in cryoglobulinaemia and macroglobulinaemia.

(2) Myelomatosis usually gives rise to a serum paraprotein in its absence some form of dysglobulinaemia remains.

(3) Occasionally paraproteinaemia is found in a number of unrelated and diverse disease states.

The investigation of many of these cases has been too incomplete to exclude myeloma. In addition they may represent early or atypical instances of the disease one case has been documented in which four years elapsed between the discovery of marked hypergammaglobulinaemia and the development of myeloma symptoms (Baker and Martin, 1959)

Clinical notes

Forty-four cases of gastrointestinal diseases were subdivided as shown in Table XVIII.

Of eleven cases of chronic peptic ulcer diagnosed clinically and supported by barium meal evidence of ulcer crater two presented with haematemesis and three with a few days' history of melaena motion. The remaining cases presented the characteristic history of epigastric pain related to meals.

The cases of ulcerative colitis in various stages of progression were of at least one year' standing with the exception of one with a three-month history of diarrhoea with blood and mucus. One case gave a history of fifteen years duration. Three of the chronic cases had been treated with steroids at some stage of the illness, but none was receiving steroids at the time of analysis. All presented with acute exacerbation of ulcerative colitis and two patients had t have total colectomy performed.

One case of Crohn s disease, proved at an appendicectomy operation, was supported by barium meal and follow-through examination.

Four of seven cases of malabsorption syndrome of varying severity presented with abdominal discomfort and related symptoms. Three of the seven had a previous partial gastrectomy One patient presented with abdominal symptoms and symptoms of peripheral neuritis, one with the clinical picture of pellagra and meg aloblastic anaemia, and one with tabes dorsalis. In four cases barium meal and follow-through examination suggested a malabsorption pattern. The xylose absorption test results ranged from 1.5 to 4.2 g per 5 hours, with a mean of 2.5 g per 5 hours. Serum carotene levels of 14 to 46 μg per 100 ml with a mean 27 μg per 100 ml were obtained. Faecal fat studies showed characteristic abnormalities.

Table XVIII Mean values of serum protein fractions i gastrointestinal diseases

Disease	Number of cases	A	α-G	α_2-G	β-G	γ-G	TG	TP
Chronic peptic ulcer	11	3.50	0.37	0.81	1.12	1.03	3.39	6.80
Early ulcerative colitis	[illegible]	4.11	0.55	0.57	0.98	0.87	2.67	6.78
Chronic ulcerative colitis	5	[illegible]47	0.35	0.88	0.95	1.75	3.91	6.50
Crohn disease	1	3.71	0.34	0.86	0.66	1.16	3.02	6.73
Malabsorption syndrome	7	2.72	0.33	0.78	0.84	1.23	3.29	6.01
Pancreatitis	4	3.48	0.37	1.08	1.15	1.56	3.93	7.30
Cholelithiasis ith acute cholecystitis	8	3.22	0.43	1.05	1.14	1.21	3.82	7.04
Cholecystitis without cholelithiasis	2	2.69	0.46	0.99	1.16	1.17	3.77	6.46
Cholelithiasis without acute cholecystitis	4	3.56	0.33	0.81	1.17	1.04	3.35	6.91

Table XIX. Clinical and laboratory data in fifteen cases of gallbladder disease

Sex	Age	Presentation	Pathological findings	Leucocyt count	E. S. R.	Cholesterol	Phospholipid / Cholesterol	Hexosamine	Alkaline phosphatase	Bilirubin
F	72	Acute	C+SC	11 100	60	188	1 04	110	20 0	0.8
F	36	Quiescent	C+CC*	3,800	4	190	1 04	85	—	—
F	76	Acut	C+SC	17,500	59	373	1 03	124	44.0	3.8
F	68	Acut	C+SC	7,200	36	238	0.92	142	14.5	1.2
M	58	Quiescent	C+CC	5,800	4	226	—	—	—	—
M	85	Acute	SC	12,200	30	—	—	—	8.9	0.6
F	63	Acute	C+SC	7 100	—	—	—	—	7.3	0.5
F	68	Acut	C+SC	17 000	27	—	—	—	4 7	0.5
F	88	Acute	C+SC	12,400	9	—	—	—	31 0	3.2
F	63	Quiescent	C+CC	6,800	4	—	—	—	—	—
F	62	Acute	C+SC	8,100	60	—	—	—	19.7	6.4
M	83	Acute	C+CC	7 100	—	—	—	—	15 7	2.8
F	81	Acute	SC	4,500	—	—	—	—	11.5	0.5
F	71	Acute	C+SC	9,300	41	—	—	—	6.6	0.5
F	70	Acut	C+SC	15,500	60	—	—	—	16.2	2.6

Cholelithiasis. Subacute cholecystitis. Chronic cholecystitis.

There were four patients with pancreatitis ranging from the mild form to the severe acute form leading to pancreatic abscess formation All cases had raised serum amylase levels. The lowest figure was 246 units in a case of chronic relapsing pancreatitis. In acute pancreatitis associated with cholelithiasis a value of 1 600 units was obtained. A higher level still occurred in the case of pancreatitis leading to pancreatic abscess formation

Fifteen cases of gall bladder diseases their presentation, and relevant laboratory data are described in Table XIX. According to pathological findings, cases were divided further into three sections acute cholecystitis with cholelithiasis, chronic cholecystitis with cholelithiasis, and acute cholecystitis with no detectable stone formation

Results

Chronic peptic ulcer failed to show a *characteristic pattern of serum proteins* This is probably due to the wide scatter of values (Table XX) One case of melaena and one of haematemesis showed decreased amounts of α_1-globulins On the other hand three cases had a raised figure One case had a superadded gastro-intestinal infection. A further case without clinical evidence of infection showed an E S R value of 103 mm per hour Therefore it is justifiable to assume that peptic ulcer itself does not give rise to an abnormal electrophoretic pattern, and that complicating factors such as bleeding and infection contribute to the wide variety of findings observed. A similar wide scatter of values was reported by Jencks, Smith and Durrum (1956) in seventeen cases of peptic ulcer

Table YY. Distribution, in standard deviations from the normal mean, of serum proteins i chronic peptic ulcer

Fraction	Standard deviations from normal mean																	
	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13
A	2	1	2	2	3	1	—	—	—	—	—	—	—	—	—	—	—	—
α₁-G	—	—	—	—	1	1	6	1	1	—	—	—	—	—	—	—	—	1
α₂-G	—	—	2	—	2	2	2	1	2	—	—	—	—	—	—	—	—	—
β-G	—	—	—	—	2	3	1	2	1	2	—	—	—	—	—	—	—	—
γ-G	—	—	1	2	4	3	1	—	—	—	—	—	—	—	—	—	—	—
TG	—	—	1	1	2	2	1	2	2	—	—	—	—	—	—	—	—	—
TP	1	—	2	—	4	2	1	1	—	—	—	—	—	—	—	—	—	—

Mean value.

The chronic ulcerative colitis cases showed a marked decrease in albumin and a moderate increase in γ-globulin, indicating a delayed response pattern with a more exaggerated drop in albumin. Thus in one case the albumin concentration was 0.87 g per 100 ml, a severe depletion characteristic of ulcerative colitis where various amounts of albumin are lost in the intestinal lumen (Steinfeld, Davidson, Gordon and Greene, 1960). The single case of recent ulcer tive colitis showed a normal pattern with low normal α- and γ-globulin values. Two cases examined by Ogryzlo, Maclachlan Dauphinee and Fletcher (1959) and sixty-one cases of active disease described by Bicks, Kirsner and Palmer (1959) showed increased $α_2$-globulin levels in addition to the findings reported here.

No conclusions can be drawn from the single case of Crohn's disease which produced a normal pattern apart from a slightly reduced concentration of β-globulins.

Malabsorption syndrome cases of varying severity revealed markedly lowered albumin and slightly lowered total protein levels unaccompanied by any characteristic globlulin alterations. This is probably indicative of a depletion pattern.

Four cases of pancreatitis, nine cases of cholelithiasis with acute cholecystitis, and two cases of cholecystitis in which no stone had been found in the gall bladder or bile duct showed the characteristic immediate response pattern to tissue necrosis lowered albumin, raised α- and total globulin levels, and a normal total protein figure. In four instances high normal to slightly raised β-globulin concentrations were found. The reason for this is obscure and phospholipid-cholesterol ratios were unavailable in many cases.

Four cases of cholelithiasis without acute cholecystitis revealed a normal pattern except for raised β-globulins. Whether cholelithiasis is associated with high serum cholesterol values thereby yielding high lipoprotein levels is not known because of the small number of cases in which lipid studies have been performed.

Clinical notes

Thirty-three cases of renal diseases were subdivided as shown in Table XXI

The mean age of five cases of acute glomerulonephritis was 20 years in which the range was from 14 to 37 years. Three patients presented with a sore throat of ten days, two weeks, and one month duration. Haematuria was present in all except one of the five cases with proteinuria. There was no history of anuria in any of the patients, but one history of oliguria was obtained. Oedema was present in each of the five cases and hypertension ranging from 140/85 to 190/110 occurred in four The blood urea levels ranged from 35 to 68 mg per 100 ml with a mean of 48 mg per 100 ml.

All patients suffering from the nephrotic syndrome manifested oedema, proteinuria, and hypercholesterolaemia. Six were of the idiopathic type while the other two were due to amyloidosis. The mean serum cholesterol content was 421 mg per 100 ml. Two cases revealed evidence of superadded infection of these, one amyloid patient had a lung abscess and one had furunculosis at the time of analysis. These are thought to account for the raised α_1-globulins.

One case of acute renal failure due to lysol ingestion was analysed.

Five cases of chronic renal failure consisted of three cases of chronic glomerulonephritis and two cases of chronic pyelonephritis. The mean blood urea level was 228 mg per 100 ml Anaemia was marked in two cases in which low normal and slightly decreased α_2-globulin concentrations were found.

Eleven cases of urinary tract infection were made up of six cases of acute pyelonephritis, three nonspecific cases, and two cases of infection associated with calculus. Leucocytosis was present in eight cases, from six of which organisms were isolated. The mean E S. R of the group was 74 mm per hour

Three cases of ureteric calculi, with no associated infection were confirmed clinically and by radiological investigations.

Table XXI Mean values of serum protein fractions in renal diseases

Disease	Number of cases	A	α –G	α –G	β–G	γ–G	TG	TP
Acute nephritis	5	3.17	0.34	0.91	0.92	1.20	3.37	6.54
Nephrotic syndrome	8	1.14	0.38	1.58	0.81	0.64	3.41	4.55
Acute renal failure	1	3.04	0.40	0.99	0.90	0.89	3.18	6.22
Chronic renal failure	5	2.96	0.52	0.80	0.94	1.12	3.18	6.14
Urinary tract infection	11	2.90	0.45	1.08	1.06	1.16	3.75	6.65
Ureteri calculi	3	3.84	0.57	0.93	1.25	1.19	3.76	7.60

Table XXII Distribution, in standard deviations from the normal mean, of serum proteins in urinary tract infection

Fraction	Standard deviations from normal mean																
	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
A	1	1	4	2	1	2	—	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	—	—	1	—	1	1	2	10	3	1	1	1
α_2-G	—	—	—	—	—	—	—	1	—	4	1	3	2	—	—	—	—
β-G	—	—	—	—	1	—	1	2	5	2	2	—	—	—	—	—	—
γ-G	—	—	—	—	—	2	3	3	5	—	—	—	—	—	—	—	—
TG	—	—	—	—	—	—	—	2	4	1	2	2	—	—	—	—	—
TP	—	—	—	1	2	3	3	2	—	—	—	—	—	—	—	—	—

Mean value.

Results

Table XXI reveals that the electrophoretic pattern in acute nephritis without anuria shows slightly decreased albumin, high normal α-globulins, and normal β- and γ-globulin levels. These findings are in agreement with earlier workers (Jencks, Smith and Durrum, 1956 Sunderman and Sunderman, 1957 Ogryzlo Maclachlan Dauphinee and Fletcher 1959) However the first two studies failed to distinguish between various stages of glomerulonephritis. The present results do not confirm the raised γ-globulin concentrations found by Reich, Coats and McDonald (1955) in a carefully planned longitudinal survey of children suffering from the disease. They reported elevated γ-globulins in the anuric as well as the nonanuric patients there was a rise of 70 t 450 % above normal values, with a clear correlation between magnitude of the rise and clinical severity of the disease. Maximum elevation took place at the point of clinical recovery Whether the present cases were much milder or single electrophoretic determinations at the times chosen failed to reveal such results is unknown, but it should be pointed out that the subjects in our survey were young adults and not children. It is concluded that acute nephritis is indistinguishable from other diseases showing an *immediate response* pattern. However quantitatively the alterations affecting albumin and the α-globulins are of a much smaller magnitude.

The nephrotic syndrome gives rise to the characteristic pattern of strongly depleted albumin, markedly raised α_2-globulin, and moderately lowered γ-globulin fractions. Increased α_1-globulins are presumably due to the two cases of infection described previously Disregarding the effects of these two cases the protein distribution suggests a 'selective' disturbance thought to arise from the altered glomerular permeability to various sized protein molecules (Chinard, Lauson, Eder Greif and Hiller 1954) together with increased fractional rates of catabolism (Gitlin, Janeway and Farr 1956)

The single pattern in acute renal failure shows the typical immediate response to tissue injury with slightly lowered total proteins.

Chronic renal failure produces a moderately lowered albumin level and slightly decreased total protein content. The distribution is thus essentially a depletion pattern with respect to albumin, typical of chronic progressive disease.

Tables XXI and XXII reveal that urinary tract infections give rise to the characteristic immediate response pattern seen in other types of acute infection.

Finally the cases with ureteric calculi show slight increases in the α_1 β- and total globulin concentrations. In the absence of supporting biochemical data it does not seem possible to classify this group with any certainty

Clinical notes

Fifteen cases of metabolic diseases wer subdivided into five groups as shown in Table XXIII All cases were selected upon clinical diagnosis. None of the alcoholic malnutrition patients showed laboratory evidence of liver disease, car diovascular disease, or any other disorders. Inadequate diet dating as far back as one or two years, was elicited in their history Both cases of anorexia nervosa were over one year' standing and again no other pparent disease was detected, part from severe malnutrion and generalized wasting

One case of obesity due to overeating has been extensively investigated for a probable endocrine aetiology all laboratory and clinical studies proved negative. The patient weighed 232 lb A hyper cholesterolaemic patient aged 44 years presented with persistently high levels of cholesterol for eighteen months. All values lay in the range 400 to 500 mg per 100 ml yet there was no evidence of atherosclerotic heart disease.

All five cases of gout were of a chronic natur which had been diagnosed earlier and were under treatment. At the time of analysis patients presented with acute exacerbation of gout showing clinical evidence of joint involvement. Without exception raised serum uric acid levels were encountered. One patient was also a diabetic.

Results

Table XXIII reveals that the serum protein electrophoretic pattern in malnutrition associated with alcoholism or with anorexia nervosa shows slightly to moder ately decreased albumin, and normal to low levels of each globulin fraction. It is therefore a depletion pattern somewhat different from the starvation pattern obtained on dehydrated but otherwise nor mal males by Taylor Mickelson and Keys (1949) in which normal to slightly increased albumin values with insignificant variations in the globulin fractions were found.

Patterns arising from the cases of obesity and hypercholesterolaemia epresent an augmented pattern In the former patient the raised α_1- and β-globulins presumably derived from hyper

Table XXIII Mean values of serum protein fractions in metabolic diseases

Disease	Number of cases	A	α–G	α–G	β-G	γ-G	TG	TP
Alcoholism with malnutrition	4	3.59	0.23	0.64	0.83	0.90	2.71	6.10
Anorexia nervosa	2	3.02	0.24	0.52	0.76	0.95	2.47	5.49
Obesity due to overeating	1	4.01	0.36	0.85	1.16	1.23	3.60	7.64
Hypercholesterolaemia	1	3.91	0.30	0.72	1.22	1.78	4.02	7.93
Gout	5	3.20	0.38	1.03	1.26	1.46	4.13	7.33

Chronic renal failure produces a moderately lowered albumin level and slightly decreased total protein content. The distribution is thus essentially a depletion pattern with respect to albumin typical of chronic progressive disease.

Tables XXI and XXII reveal that urinary tract infections give rise to the characteristic immediate response pattern seen in other types of acute infection.

Finally the cases with ureteric calculi show slight increases in the α_1 β- and total globulin concentrations. In the absence of supporting biochemical data it does not seem possible to classify this group with any certainty

Clinical notes

Seventy-two obstetric patients were chosen from the King Edward Memorial Hospital for Women for inclusion in the survey. The main types of conditions and their subdivisions are outlined in Table XXIV.

Normal pregnancy cases were subdivided into three groups: 0 to 12 weeks pregnancy, 13 to 24 weeks pregnancy and 25 to 40 weeks pregnancy. The term of pregnancy was ascertained by clinical examination and menstrual history of the patient. All were regular attendants of the antenatal clinic, and those cases were discarded in which any doubts were aroused of complicating disease.

Cases with mild pre-eclamptic toxaemia were selected according to the following criteria: (a) blood pressure of, or greater than, 140/90 after 24 weeks pregnancy (b) oedema, especially of the face or finger and (c) albuminuria. All patients satisfied criterion (a). Four revealed severe oedema, eighteen had moderate oedema, while one presented with slight oedema. Three cases showed slight albuminuria.

Patients with essential hypertension were selected according to the blood pressure reading. They had repeated tensions of at least 140/90 at, or before, the 24th week of pregnancy. Cases in which pre-eclamptic toxaemia complicated essential hypertension were discarded.

In the miscellaneous group the following cases were included: two cases of severe anaemia of pregnancy (in one of the iron-deficient type the haemoglobin level was 7.9 g %, in the other of the macrocytic and iron-deficient type the

Table XXIV Mean values of serum protein fractions in obstetric conditions

Condition	Number of cases	A	α_1–G	α_2–G	β–G	γ–G	TG	TP
Normal pregnancy								
0—12 weeks	4	3.77	0.59	0.80	0.83	0.93	2.85	6.62
13—24 weeks	8	3.58	0.38	0.87	1.05	0.98	3.28	6.86
25—40 weeks	16	3.09	0.45	0.91	1.25	0.89	3.50	6.59
Pre-eclamptic toxaemia	28	2.93	0.45	0.88	1.23	0.89	3.45	6.38
Essential hypertension	9	3.14	0.38	0.90	1.08	0.93	3.29	6.43
Normal comparison figures	9	3.42	0.39	0.87	1.05	0.79	3.11	6.53
Complications of pregnancy								
Severe anaemia of pregnancy	2	3.31	0.46	0.93	1.02	0.81	3.22	6.53
Ante-partum haemorrhage	2	3.03	0.43	0.97	1.13	0.69	3.22	6.25
Twin pregnancy	1	2.83	0.39	1.05	1.22	0.93	3.61	6.44
Myxoedema with pregnancy	1	3.68	0.61	1.20	1.58	1.30	4.69	8.37
Chronic nephritis with pregnancy	1	2.17	0.28	1.08	1.46	1.31	4.13	6.30

Data from 9 cases of normal pregnancy of the same duration.

lipoproteinaemia in spite of the high normal cholesterol level and the normal free serum lipid content.

The protein distribution in acute gout is characterized by a depletion in albumin and slight increments in α- and β-globulins It is thought that it is a fusion of an immediate response to tissue injury with an augmented response manifested in the raised β-globulin fraction. The significant elevation of β-globulins confirms the observation of Ogryzlo Mac lachlan, Dauphinee and Fletcher (1959) It is interesting to find an abnormality in the major lipoprotein fraction in this disease and to note that a similar elevation has been observed in atherosclerosis and in diabetes complicated by acidosis.

level was 10.2 g %) two cases of accidental ante partum haemorrhage one case of twin pregnancy with early hydramnios one case of myxoedema occurring in pregnancy and one case of chronic nephritis complicating pregnancy

Results

The observations recorded in Tables XXIV and XXV show that the serum protein pattern in normal pregnancy is characterized by an increasing degree of quantitative changes in the various fractions as the time of delivery is approached. Until the twelfth week there is a tendency for both the albumin and γ-globulin fractions to reach low normal values. During the next twelve weeks this trend is maintained while the -globulin fraction attains slightly increased values and the a_2- and β-globulins approach high normal figures.

After the twenty-fifth week hypoalbuminaemia becomes pparent, the a_1-globulins markedly increase, the a_2-globulins still show high normal values, the β-globulins become slightly elevated, and the γ-globulins drop to low normal amounts. Thus throughout the whole term of pregnancy the balance between albumin and globulins is such that significant hyperglobulinaemia and hyperproteinaemia occur at no stage, despite the variations which all individual fractions undergo.

These changes are generally in agreement with previous publications (Coryell, Beach Robinson, Macy and Mack, 1950 Mack, 1955) except for failure to confirm a definite increase in the a_2-globulins and a decrease in the antibody fraction. (Table XXV indicates that 25 % of cases showed raised a_2-globulins, while 31 % showed decreased γ-globulin levels.)

Without undertaking an exhaustive analysis of the protein metabolism associated with normal pregnancy the present results suggest that the distribution is qualitatively unique. Thus t fails to conform to previously described patterns such as augmented, depleted, immediate, or delayed responses to stimuli. Two possibilities remain firstly it may be a mixed pattern arising from addition of two or more of the above responses, or secondly it may be a selective pattern similar in nature to that described in the nephrotic syndrome.

Examination of the hypoalbuminaemia, raised a_1-globulins, and high normal a_2-globulins recalls the characteristic immediate response pattern to traumatic injury irrespective of its nature. Whether this response is occasioned by the invasive activity of the trophoblast and later by the placenta is mere speculation Neuweiler (1948) related the elevated a-globulins to the presence of increased amounts of hypertensinogen found even in normal pregnancy

The possibility that depletion or excess may play a significant role in the pregnancy pattern has been previously studied and attempted correlations have been made with a wide variety of physiological and biochemical entities. Thus the ascription of hypoalbuminaemia to retardation of albumin synthesis in the face of increased utilization has not been supported by dietary surveys and liberal administration of protein-rich food. Also the diluting effect of an increased blood volume during term, despite a relatively higher amount of circulating protein, has been invoked.

There is considerable evidence (Peters, Heinemann and Man, 1951) that the

Table XXI Distribution, in standard deviations from the normal mean, of serum protein fractions in obstetric conditions

Normal pregnancy to the 24th week

Fraction	Standard deviations from normal mean															
	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
A	—	—	—	3	6	2	1	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	2	1	1	5	2	1	—	—	—	—	—
α_2-G	—	—	—	—	—	2	2	6	1	1	—	—	—	—	—	—
β-G	—	—	—	—	1	2	5	3	1	—	—	—	—	—	—	—
γ-G	—	—	—	1	7	2	1	1	—	—	—	—	—	—	—	—
TG	—	—	—	1	2	3	2	3	1	—	—	—	—	—	—	—
TP	—	—	—	1	5	3	2	1	—	—	—	—	—	—	—	—

Normal pregnancy from the 25th week to delivery

Fraction	Standard deviations from normal mean															
	−6	−5	−4	3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
A		2	9	5	—	—		—	—	—		—	—	—	—	—
α -G	—	—	—	—	—	—		1	—	2	4	6	2	—	1	—
α -G		—		—	—	2	4	6	2	1		1	—	—	—	—
β-G	—	—	—	—	—	1	1	1	5	6	1	1	—	—	—	—
γ-G	—	—	1	4	8	2	1		—	—		—	—	—	—	—
TC	—					3	5	4	2	1	1		—		—	—
TP				4	7	4	1	—	—	—	—	—	—	—	—	—

Pre-eclamptic toxaemia

Fraction	Standard deviations from normal mean															
	6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10
A	2	7	13	6			—	—	—	—	—		—		—	—
α -G	—	—	—	—	—		—	—	3	2	13	4	1	3	—	2
α_2-G	—		—	—	1	7	6	5	7	—	2	—	—	—	—	—
β-G		—	—	—	—	—	5	5	10	6	2	2	—	—	—	—
γ-G	—		1	8	9	7	3	—	—	—	—	—	—	—	—	—
TG	—	—	—	—	3	5	6	3	8	3	—	—	—	—	—	—
TP	—	1	3	8	6	6	4	—	—	—	—	—	—	—	—	—

Mean value.

level was 10.2 g %) two cases of accidental ante-partum haemorrhage one case of twin pregnancy with early hydramnios one case of myxoedema occurring in pregnancy and one case of chronic nephritis complicating pregnancy

Results

The observations recorded in Tables XXIV and XXV show that the serum protein pattern in normal pregnancy is characterized by an increasing degree of quantitative changes in the various fractions as the time of delivery is approached. Until the twelfth week there is a tendency for both the albumin and γ-globulin fractions to reach low normal values. During the next twelve weeks this trend is maintained while the α_1-globulin fraction attains slightly increased values and the α_2- and β-globulins approach high normal figures.

After the twenty-fifth week hypoalbuminaemia becomes apparent the α globulins markedly increase, the α_2-globulins still show high normal values, the β-globulins become slightly elevated, and the γ-globulins drop to low normal amounts. Thus throughout the whole term of pregnancy the balance between albumin and globulins is such that significant hyperglobulinaemia and hyperproteinaemia occur t no stage, despit the variations which all individual fractions undergo.

These changes are generally in agreement with previous publications (Coryell, Beach, Robinson, Macy and Mack, 1950 Mack, 1955) except for a failure t confirm a definite increase in the α_1-globulins and a decrease in the antibody fraction. (Table XXV indicates that 25 of cases showed raised α_1-globulins, while 31 % showed decreased γ-globulin levels.)

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The possibility that depletion or excess may play a significant role in the pregnancy pattern has been previously studied and attempted correlations have been made with a wide variety of physiological and biochemical entities. Thus the ascription of hypoalbuminaemia to retardation of albumin synthesis in the face of increased utilization has not been supported by dietary surveys and liberal administration of protein-rich food. Also th diluting effect of an increased blood volume during term, despite a relatively higher amount of circulating protein, has been invoked.

There is considerable evidence (Peters, Heinemann and Man, 1951) that the

[illegible]	[illegible]	[illegible]			Cholesterol			Phospholipid / Cholesterol	
	[illegible]	Range	Mean	Number abnormal	Range	Mean	Number abnormal	Range	Mean
[illegible] pregnancy [illegible]	5	[illegible]–120	111	0	211–265	246	0	0 77–0.99	0 87
[illegible]	–	103–139	119	1	195–304	268	2	0.93–1.34	1 14
[illegible] ma	23	113–154	125	7	198–382	285	8	0 75–1 48	1 07

serum lipids undergo a progressive in crease during the last two trimesters of pregnancy In this elevation the total *cholesterol* content and *phospholipids* participate proportionately while main taining their normal interrelation. This has been confirmed in a limited number of cases (Table XXVI) Two of seven cases in the last trimester group showed abnormally high cholesterol and phospho-lipid values the mean cholesterol and phospholipid concentration during the last two trimesters are significantly raised, yet their ratio remains normal It there-fore seems that a simple pathological ex cess of certain constituents cannot account for the observed results.

There is also the puzzling question of decreased maternal antibodies during the last months of pregnancy That this is not entirely a simple *depletion effect is proved* by the γ-globulin concentration in cord blood and the foetus. It therefore is wise to assume that the normal pregnancy pattern is not the result of fusion of re-sponses but arises from selective forces operating on the protein pool through various [illegible] glands such as thyroid ovari

The cases of pre-eclamptic toxa failed to differ significantly from changes observed in the final trimest the normal group The reason presum lies in the mildness of the cases so the previously described exaggeratio the normal pregnancy pattern (M 1955) failed to become apparent. significant differences were obtained tween nine cases of essential hyperten as a complication and the normal p nancy group (The latter figures w calculated from the 13 to 40 weeks gro in proportion to their representation the hypertensive group)

Two cases of ante-partum haemorrh gave rise to a similar pattern to the norn cases in addition to slightly raised globulin and slightly lowered γ-globu fractions Owing however to such *small number of cases the significance* this finding is questionable. In one ca of twin pregnancy which was complicat by early hydramnios, marked hypoalb naemia without undue hyperglobulu aemia was found.

The single case of chronic nephrit complicating pregnancy failed to reve any new features apart from a low a

bumin level, consistent with the proteinuria, and a normal α_1-globulin fraction. The myxoedematous patient showed high α- and β-globulin concentrations, the latter result being a somewhat consistent finding in myxoedema. The final two cases of severe anaemia of pregnancy conform to the normal pregnancy pattern.

It is concluded that the serum protein pattern in pregnancy reflects a unique and selective change occurring in the various fractions as influenced by certain endocrine glands with the effect of maintaining and aiding the development of the foetus. Many of the complications failed to reveal significant changes, although earlier reports indicated that pre eclamptic toxaemia produced quantitative alterations in the same qualitative normal pregnancy pattern. Some of the medical diseases complicating pregnancy yield a distribution in which the dominating feature of the disease is superimposed on the normal to form a fused type of pattern.

Table XXVI Mean values of biochemical estimations in obstetric conditions

Condition	Number of cases	Hexosamine			Cholesterol			Phospholipid / Cholesterol		
		Range	Mean	Number abnormal	Range	Mean	Number abnormal	Range	Mean	Number abnormal
Normal pregnancy										
13—24 weeks	3	96—120	111	0	211—265	246	0	0.77–0.99	0.87	0
25—40 weeks	7	*108—139*	*119*	1	*195—301*	*268*	2	*0.95–1.31*	*1 14*	2
Pre-eclamptic toxaemia	23	113—154	125	7	198—382	285	8	0.75–1 48	1.07	4

serum lipids undergo a progressive increase during the last two trimesters of pregnancy In this elevation the total cholesterol content and phospholipids participate proportionately while maintaining their normal interrelation. This has been confirmed in a limited number of cases (Table XXVI) Two of seven cases in the last trimester group showed abnormally high cholesterol and phospholipid values the mean cholesterol and phospholipid concentration during the last two trimesters are significantly raised, yet their ratio remains normal. It therefore seems that a simple pathological excess of certain constituents cannot account for the observed results

There is also the puzzling question of decreased maternal antibodies during the last months of pregnancy That this is not entirely a simple depletion effect is proved by the γ-globulin concentration *in cord* blood and the foetus. It therefore is wise to assume that the normal pregnancy pattern is not the result of fusion of responses but arises from selective forces operating on the protein pool through various endocrine glands such as thyroid, ovaries, and placenta.

The cases of pre-eclamptic toxaemia failed to differ significantly from the changes observed in the final trimester of the normal group The reason presumably lies in the mildness of the cases so that the previously described exaggeration of the normal pregnancy pattern (Mack 1955) failed to become apparent. No significant differences were obtained between nine cases of essential hypertension as a complication and the normal pregnancy group (The latter figures were calculated from the 13 to 40 weeks groups in proportion to their representation in the hypertensive group)

Two cases of ante partum haemorrhage gave rise to a similar pattern to the normal cases in addition to slightly raised *a* globulin and slightly lowered γ-globulin fractions. Owing however to such a small number of cases the significance of this finding is questionable. In one case of twin pregnancy which was complicated by early hydramnios marked hypoalbuminaemia *without undue hyperglobulinaemia* was found

The single case of chronic nephritis complicating pregnancy failed to reveal any new features apart from a low al-

bumin level, consistent with the proteinuria, and a normal α_1-globulin fraction. The myxoedematous patient showed high α- and β-globulin concentrations, the latter result being a somewhat consistent finding in myxoedema. The final two cases of severe anaemia of pregnancy conform to the normal pregnancy pattern.

It is concluded that the serum protein pattern in pregnancy reflects a unique and selective change occurring in the various fractions as influenced by certain endocrine glands with the effect of maintaining and aiding the development of the foetus. Many of the complications failed to reveal significant changes, although earlier reports indicated that pre-eclamptic toxaemia produced quantitative alterations in the same qualitative normal pregnancy pattern. Some of the medical diseases complicating pregnancy yield a distribution in which the dominating feature of the disease is superimposed on the normal to form a fused type of pattern.

Clinical notes

Thirty three cases of endocrine disorders were subdivided into the groups shown in Table XXVII

Seven thyrotoxic cases were selected by clinical diagnosis and all were confirmed by their basal metabolic rates and *radioactive* iodine uptakes. Patients with myxoedema presented with typical symptoms their protein-bound iodine (P B I) *levels were decreased and cholesterol* levels were increased in all cases. Thyroglobulin antibody agglutination tests (T A. A.) using the haemagglutination technique (Roitt and Doniach, 1958) were also carried out. Of the remaining thyroid cases, two presented with the clinical picture of a mild nonspecific thyroiditis. The first had been treated with steroids and was found to have Riedel's thyroiditis on histological examination This patient had a negative T A. A titre. The second was an undiagnosed *case of thyroiditis histological* examination failed to point to any definite diagnosis One of the three cases presenting with goitre was undiagnosed, while confirmation of Hashimoto's struma was made in the others by biopsy The relevant findings are summarized in Table XXVIII

Eleven cases of clinically diagnosed diabetes mellitus were included of these, three had an infected ulcer on the foot, while one had a urinary tract infection. *All the* diabetics were elderly obese types the majority having a long history of disease. Cases of acromegaly adreno*genital syndrome, Cushing's syndrome,* and hypopituitary hypogonadism made up the total number

Results

As indicated in Table XXVII thyrotoxic patients failed to reveal a characteristic protein pattern the mean albumin concentration falling in the low normal range. Normal distributions have also been recorded by Jencks Smith and Durrum (1956) Hyperglobulinaemia was

Table XXVII Mean values of serum protein fractions in endocrine diseases

Disease	Number of cases	A	α -G	α -G	β-G	γ-G	TG	TP
Thyrotoxicosis	7	3.48	0.33	0.84	1 02	1.24	3.43	6.91
Myxoedema	9	3.75	0.35	0.97	1.23	1 31	3.86	7.61
Hashimoto disease	2	3.77	0.37	1 11	1 16	2.15	4 79	8.56
Uncomplicated diabetes	7	3.50	0.31	0.86	1 03	1 18	3.38	6.88
Diabetes with infection	4	3.25	0.36	0.99	1 12	1.21	3.71	6.96
Acromegaly	1	3.38	0.30	0.66	1.02	1.06	3.04	6.42
Adrenogenital syndrome	1	4.62	0.32	0.69	1 43	1.21	3.65	8.27
Cushing syndrome	1	4.25	0.31	0.99	1 15	1 10	3.55	7.80
Hypopituitary hypogonadism	1	4.03	0.24	0.66	0.91	1.25	3.06	7 09

Table XXVIII Values of biochemical estimations in thyroid diseases

Case	Sex	Age	Diagnosis	P.B.I.	T.A.A.	γ-G	Cholesterol
1	F	70	Myxoedema	0.3	Negative	1.58	346
2	F	43	Myxoedema	1.0	Negative	1.48	322
3	F	68	Myxoedema	1.6	Negative	1.00	400
4	F	63	Myxoedema	0.8	1 25,000	1.14	332
5	F	37	Subthyroid cretin	2.2	1 5	1.43	307
6	M	74	Secondary myxoedema (cause unknown)	2.4	Negative	1.39	—
7	F	80	Myxoedema	1.5	1 25,000	1.43	464
8	F	64	Myxoedema	0.8	Negative	1.07	320
9	F	55	Myxoedema	0.6	1 2,500	1.27	330
10	F	24	Undiagnosed thyroiditis	—	1 2,500	1.11	—
11	F	31	Riedel' thyroiditis	—	Negative	1.46	—
12	F	49	Hashimoto struma	—	1 250,000	2.70	—
13	F	82	*Hashimoto struma*	*4.0*	*1 2,500,000*	*1.39*	298
14	F	20	Undiagnosed goitre	13.4	1 2,500	0.82	—

Thought to be predominantly thyroglobulin.

shown by the myxoedematous cases due to increased a_2- and β-globulin levels, and high normal γ-globulins. These findings, together with the high cholesterol concentrations, suggest a pathological serum lipoprotein distribution so that the disease manifests itself as an augmented type of protein pattern. On the other hand, Jencks, Smith and Durrum (1956) found a normal electrophoretic distribution in the three patients they examined.

The two highest T. A. A. titres and the two highest γ-globulin levels were found in cases 12 and 13 with Hashimoto disease. In the two undiagnosed cases normal γ-globulin concentrations were obtained despite elevated T. A. A. titres. In Riedel' struma the T. A. A. titre was negative and the γ-globulin level normal.

Although Hashimoto's disease was described in 1912, it was much later that the occurrence of raised γ-globulin concentrations, and increased thymol and zinc sulphate turbidities were reported (Luxton and Cooke, 1956. Doniach and Hudson, 1957). In the latter study a mean γ-globulin level of 2.13 g per 100 ml was recorded from eleven cases, and this suggests that large goitres were associated with the most striking electrophoretic changes. Because of the small number of cases in the present study it is not possible to attempt a correlation between titre and γ-globulin concentration. It is interesting to observe that three cases of primary myxoedema produced a positive titre, thus raising the possibility that they may be the end result of clinically undiagnosed cases of Hashimoto disease.

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Except for a normal albumin level, the group labelled "Hashimoto's Disease" with positive agglutination results reveals a mixture of immediate and delayed reaction patterns such as seen previously in bronchial asthma. Of the non-thyroid patients, a normal electrophoretic pat

tern was observed in uncomplicated diabetes, in essential agreement with an earlier publication (Schneider Lewis and McCullagh 1946) in which cases of mild untreated diabetes were examined. However these authors found raised β-globulin levels in patients with uncomplicated diabetic acidosis which probably arise from a β-lipoprotein elevation (Barr and Russ, 1951) Sunderman and Sunderman (1957) described normal patterns in their subjects, while Jencks, Smith and Durrum (1956) reported a normal distribution with a tendency to high β-globulin concentrations in twelve patients. On the other hand, Seibert, Seibert, Atno and Campbell (1947) observed increased β-globulins in their diabetic subjects. In the present study diabetics with superimposed infection produced the characteristic immediate response pattern to acute infection.

The single case of acromegaly gave rise to a slightly decreased albumin content in an otherwise normal protein pattern. Jencks, Smith and Durrum (1956) found normal protein patterns in their two cases. A markedly elevated β-globulin fraction was observed in the patient with adrenogenital syndrome. In the case with Cushing's syndrome, a slightly increased α_1-globulin and high normal β-globulin fraction were the only abnormal signs. Finally a normal pattern was observed in hypopituitary hypogonadism.

Clinical notes

Forty patients with liver diseases were subdivided into five groups as shown in Table XXIX.

Cases of cirrhosis of the liver were selected on clinical diagnosis. Two were associated with beri beri in one of them liver biopsy revealed fatty infiltration and early portal cirrhosis, while the other presented with hepatomegaly and ascites. In fourteen cases (70) positive evidence of an alcoholic history was obtained. Altogether ten patients had ascites, six showed spider naevi, six had a palpable spleen, oesophageal varices were demonstrated in four cases, and one presented with haematemesis. Two cases of cardiac cirrhosis presented with a long history of congestive cardiac failure with hepatomegaly One patient presented with a history of infectious hepatitis, hepatomegaly ascites, and spider naevi liver biopsy revealed postnecrotic scarring a small amount of fatty change, and mild portal fibrosis. One case of cirrhosis was associated with a hepatoma. This has been included here because the dominant clinical picture was cirrhotic. In contrast, the other case with a hepatoma encountered in the survey had secondary deposits and resembled clinically secondary carcinoma.

A case of acute hepatic necrosis caused by Marsalid" was confirmed by autopsy findings.

The hepatitis cases were divided into two groups of acute hepatitis and one group of chronic hepatitis receiving steroids. The clinically diagnosed cases of acute hepatitis were all jaundiced, showing bilirubin levels ranging from 1.2 t 15 4 mg per 100 ml. The question of whether they should be regarded as a homogeneous group of varying severity or as a heterogeneous group was resolved by separating them into two sections on the basis of the S. G O T — alkaline phosphatase ratio (Latner and Smith, 1958) The group having values over the arbitrary value of 6 were denoted as classical infectious hepatitis, while those less than 6 were designated as probable cholangiolitic types. This separation is purely empirical and is based on neither histological or aetiological criteria. Only

Table XXIX Mean values of serum protein fractions in hepatic diseases

Disease	Number of cases	A	α_1–G	α_2–G	β–G	γ–G	TG	TP
Hepatic cirrhosis	20	2.31	0.30	0.60	0.92	2.51	4.34	6.65
Acute hepatic necrosis	1	3.14	0.23	0.31	0.99	1.97	3.10	6.24
Acute hepatitis (cholangiolitic)	6	3.57	0.36	0.65	1.22	1.59	3.82	7.40
Acute hepatitis (chemical)	9	3.55	0.38	0.82	1.25	1.99	4.41	7.96
Chronic active hepatitis (steroid-treated)	4	3.68	0.33	0.78	1.16	2.37	4.63	8.31

Table XXX Distribution in standard deviations from the normal mean, of serum protein fractions in hepatic cirrhosis

Fraction	Standard deviations from normal mean																					
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14
A	5	5	4	3	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
α –G	—	—	—	—	—	2	3	5	5	1	4	—	—	—	—	—	—	—	—	—	—	—
α –G	—	—	—	—	2	7	4	2	2	3	—	—	—	—	—	—	—	—	—	—	—	—
β-G	—	—	—	2	—	1	5	2	2	5	2	1	—	—	—	—	—	—	—	—	—	—
γ-G	—	—	—	—	—	—	—	—	—	—	2	5		—	1	2	—	—	2	3	2	1
TG	—	—	—	—	—	—	—	—	2	3	2	4	1	1	2	3	1	1	—	—	—	—
TP	—	—	—	2	1	4	4	3	3	3	—	—	—	—	—	—	—	—	—	—	—	—

Mean value.

in one case was a definite history of chlor promazine medication established prior to jaundice.

Four cases of *chronic active infectious* hepatitis, similar to those described by Saint King Joske and Finckh (1953) were all confirmed by liver biopsy find ings. Evidence of the L. E. cell phe-nomenon *described by Joske and King* (1955) and reported in cases by Mackay Taft and Cowling (1956) and Ogryzlo Maclachlan Dauphinee and Fletcher (1959) was found in one case on at least one occasion.

Results

Tables XXIX and XXX indicate that cirrhosis produces a very marked de crease in albumin a *low normal α globulin* fraction normal $α_{1}$- and β globulin levels and a very marked in crease in γ-globulins. This resulted in marked hyperglobulinaemia but only *low normal* total protein concentrations. Characteristic aberrations of this type have been *documented previously* (Church and Blackburn 1954 Sunder man and Sunderman, 1957 Ogryzlo Maclachlan Dauphinee and Fletcher 1959) Similar changes were observed in *diffuse hepatic fibrosis by Owen and* Robertson (1956) however no specific alterations were produced by seven cases of cardiac cirrhosis, and in a precirrhotic group (patients with chronic alcoholism *and hepatomegaly) and pattern* was mainly normal with a tendency to low normal albumin and raised γ-globulin fractions In the present *study the dis* tribution may be described as a delayed response pattern with a tendency towards a depletion pattern (grossly reduced al bumin and *low normal α -globulin)* which is due to the decreased ability of the dis-eased liver to synthesize albumin and some globulins

Acute *hepatic necrosis* appears to con *form to the mixed* type of distribution in which a depletion pattern is superimposed on a delayed response *pattern. Similar* results were recorded by Owen and Ro-bertson (1956)

Both acute hepatitis groups revealed a low normal albumin figure, normal *α globulins* and slightly elevated α and β-globulins. The γ-globulins were high

normal in the first section and markedly elevated in the second. Although the patterns bear obvious similarities, the severity of classical hepatitis, compared with the cholangiolitic type, is reflected in the higher γ-globulin levels. This result may be compared with the view of Owen and Robertson (1956) who consider the γ-globulin concentration to be prognostically significant in acute hepatitis. Similar findings were first reported by Gray and Barron (1943) followed by Ricketts and Sterling (1949) and Franklin, Bean, Paul Routh, de la Huerga and Popper (1951) A study by Satoskar Lewis and Gaitonde (1954) describes essentially similar changes with depletion of the α-globulin in severe cases of viral hepatitis. Thus acute hepatitis, like other viral infections, results in a delayed response pattern.

The four cases of chronic active hepatitis yielded comparable results with higher γ-globulin levels despite steroid therapy However levels of 4.0 to 8.6 g per 100 ml reported by Ogryzlo, Maclachlan, Dauphinee and Fletcher (1959) in so-called lupoid hepatitis with positive L. E. phenomenon were not obtained, the highest value found being 2.86 g per 100 ml

Table XXX Distribution, in standard deviations from the normal mean, of serum protein fractions in hepatic cirrhosis

Fraction	Standard deviations from normal mean																					
	−8	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13	+14
A	5	5	4	3	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	—	2	3	5	5	1	4	—	—	—	—	—	—	—	—	—	—	—
α-G	—	—	—	—	2	7	4	2	2	3	—	—	—	—	—	—	—	—	—	—	—	—
β-G	—	—	—	2	—	1	5	2	2	5	2	1	—	—	—	—	—	—	—	—	—	—
γ-G	—	—	—	—	—	—	—	—	—	—	2	5	2	—	1	2	—	—	2	3	2	1
TG	—	—	—	—	—	—	—	—	2	3	2	4	1	1	2	3	1	1	—	—	—	—
TP	—	—	—	2	1	4	4	3	3	3	—	—	—	—	—	—	—	—	—	—	—	—

Mean value.

in one case was a definite history of chlorpromazine medication established prior to jaundice

Four cases of chronic active infectious hepatitis similar to those described by Saint, King Joske and Finckh (1953) were all confirmed by liver biopsy findings. Evidence of the L. E. cell phenomenon described by Joske and King (1955) and reported in cases by Mackay Taft and Cowling (1956) and Ogryzlo Maclachlan Dauphinee and Fletcher (1959) was found in one case on at least one occasion.

Results

Tables XXIX and XXX indicate that cirrhosis produces a very marked decrease in albumin a low normal α_1 globulin fraction, normal α_1 and β-globulin levels, and a very marked increase in γ globulins. This resulted in marked hyperglobulinaemia but only low normal total protein concentrations Characteristic aberrations of this type have been documented previously (Church and Blackburn 1954 Sunderman and Sunderman 1957 Ogryzlo, Maclachlan, Dauphinee and Fletcher 1959) Similar changes were observed in diffuse hepatic fibrosis by Owen and Robertson (1956) however no specific alterations were produced by seven cases of cardiac cirrhosis, and in a precirrhotic group (patients with chronic alcoholism and hepatomegaly) and pattern was mainly normal with a tendency to low normal albumin and raised γ-globulin fractions. In the present study the distribution may be described as a delayed response pattern with a tendency towards a depletion pattern (grossly reduced albumin and low normal α_1-globulin) which is due to the decreased ability of the diseased liver to synthesize albumin and some globulins.

Acute hepatic necrosis appears to conform to the mixed type of distribution in which a depletion pattern is superimposed on a delayed response pattern. Similar results were recorded by Owen and Robertson (1956)

Both acute hepatitis groups revealed a low normal albumin figure normal α_1-globulins, and slightly elevated α and β-globulins. The γ-globulins were high

thritis were treated w th steroids prior to testing The mean E. S R. was 47 mm per hour (range 23 to 105) All cases showed radiological evidence of long-standing disease, while clinical and laboratory data suggested continuous activity of the rheumatoid process.

Both cases of ankylosing spondylitis, one of two years and the other of three years' standing revealed clinical and laboratory evidence of active disease. The patients with Reiter' syndrome were diagnosed on the clinical basis of subacute polyarthritis, urethritis, and con junctivitis.

All cases of rheumatic fever presented with a history of sore throat followed by joint pain and swelling, fever and cardiac involvement two cases showed characteristic skin lesions. All four patients had high sedimentation rates, and the antistreptolysin O titres (A. S O T) ranged from 125 to 1,250 units.

All four cases of chronic rheumatic heart disease selected gave a history of rheumatic fever and showed evidence of rheumatic valvular disease. However they were free of congestive cardiac failure at the time of analysis.

A group of four patients presented with pain and swelling of one or more joints following an infectious episode

Case 1 presented with joint involve ment two weeks after an upper respiratory tract infection The E S R was 59 mm per hour ther was no leucocytosis, and no clinical evidence of cardiac involve ment The A. S. O T was 50 units and the C-reactive protein (C. R. T) result was + +

Case 2 presented with fever and pain in the left hip joint following a furuncle on the left arm two weeks previously Blood culture was sterile on three re peated examinations. X-ray failed to show any bone involvement. There was a leucocytosis of 18,200 The E. S R. was 52 mm per hour C. R. T was ++++ and the A. S O T was 50 units.

Case 3 presented with joint involve ment after an episode of upper respiratory tract infection. There was no leucocytosis. The E. S R. was 110 mm per hour the C. R. T was +++ and the A. S. O T was 125 un ts.

Case 4 presented with fever and joint involvement three weeks after an episode of infected haemorrhoids. Leucocytosis was absent. Blood culture showed haemolytic streptococci. The E. S R. was 27 mm per hour C. R. T was ++++ and A. S. O T was 125 units.

N definite diagnosis has been established in these cases, so the term post infective arthropathy" was applied to the group.

Fou cases of polymyositis have been included following clinical diagnosis by the same honorary physician. Muscle biopsy was not performed on any of the cases, and no L. E. cell phenomenon was observed. All cases had high red cell sedimentation rates nd improved dramatically on steroid therapy

Seven clinically diagnosed cases of osteoarthritis were used as a comparison for the rheumatoid arthritis patients. All revealed X-ray evidence of degenerative arthritis.

Both patients with disseminated lupus erythematosus presented with arthralgia, characteristic face rash, and mild anae mia. They were found to have numerous L. E. cells in the blood. Six further cases had been diagnosed for many years and were being treated with steroids.

A single case of polyarteritis nodosa presented with the clinical picture of acute appendicitis. Pathology exami-

Clinical notes

Seventy cases of rheumatic and collagen diseases have been subdivided as shown in Table XXXI

Of the patients with rheumatoid arthritis who were not undergoing steroid treatment 62 % were chronic cases of one to thirty years duration (mean twelve years) The remainder were of recent onset. All the patients were receiving salicylates at the time of analysis. Every one of the chronic cases showed exacerbation of the rheumatic process the majority had received gold therapy a few months prior to analysis and one had been treated with butazolidine. The mean E S R. value of the chronic cases was 82 mm per hour (range 29 to 123) and for the more recent cases 71 mm per hour (range 26 to 115) Rose and Ball tests were carried out in eight of the sixteen chronic cases three showed negative results, two showed 1 512 titres, and the remainder showed 1 16 1 32 and 1 128 titres. Eight of the new cases yielded the following results three were negative, one was 1 64 two were 1 128, one was 1 256 and one was 1 2 048 All except one of the long-standing cases showed X ray evidence of rheumatoid arthritis in one or more of their joints, while each of the recent cases presented with clinical evidence of joint involvement. Since both types of active disease failed to show any significant difference in their electrophoretic patterns, they were grouped together for statistical purposes.

Six cases of chronic rheumatoid ar

Table XXXI Mean values of serum protein fractions in rheumatic diseases

Disease	Number of cases	A	α_1-G	α -G	β-G	γ-G	TG	TP
Rheumatoid arthritis (non-steroid treated)	25	2.99	0.42	1.16	1.20	1.85	4.63	7.62
Rheumatoid arthritis (steroid treated)	6	3.00	0.39	1.03	1.17	1.02	3.61	6.61
Ankylosing spondylitis	2	2.45	0.55	1.37	1.45	2.04	5.41	7.86
Reiter's syndrome	5	3.69	0.46	1.12	1.29	1.49	4.36	8.05
Rheumatic fever	4	3.09	0.46	1.11	1.17	2.34	5.08	8.17
Chronic rheumatic heart disease	4	3.55	0.33	0.90	1.10	1.90	4.25	7.80
Post infective arthropathy	4	2.87	0.45	1.16	1.02	1.07	3.70	6.57
Polymyositis	4	3.17	0.46	1.21	1.16	1.09	3.91	7.08
Osteoarthritis	7	3.78	0.30	0.77	1.01	0.98	3.06	6.84
Disseminated lupus erythematosus (non-steroid treated)	2	2.10	0.30	0.68	0.79	2.28	4.05	6.15
Disseminated lupus erythematosus (steroid treated)	6	3.23	0.32	0.89	1.05	2.24	4.50	7.73
Polyarteritis nodosa	1	3.12	0.43	1.23	0.85	4.30	6.81	9.93

correlation with clinical activity of the disease. High hexosamine concentrations were encountered in seven out of ten cases analysed in the present study the mean level was 152 mg per 100 ml.

It is concluded that the electrophoretic distribution in rheumatoid arthritis may be described as a combination of the immediate and delayed response patterns. This appears t support the hypothesis put forward by various investigators (Marmont, 1948 Curletto and Magistretti, 1949 Wallis, 1950 Berglund, Nordenson and Olhagen, 1951 Layani Bengui and De Mende, 1952) that the disease is an inflammatory process which stems from an ineffective antigen-antibody reaction (perhaps of an autoimmune nature) leading to reticuloendothelial hyperplasia. Elevated γ-globulins may be the expression of this hyperactivity

The group of steroid-treated rheumatoid arthritic cases showed much the same distribution as above except that the γ-globulins remained normal. This accords with bservations by Bonomo (1957)and Ogryzlo, Maclachlan, Dauphinee and Fletcher (1959) The cases of ankylosing spondylitis produced the rheumatoid arthritic pattern.

Reiter's syndrome gave rise t a low normal albumin, a very marked rise in α_1-globulins, a moderate increase in α_2 and β-globulins, and a high normal γ-globulin level, in agreement with Ogryzlo Maclachlan Dauphinee and Fletcher (1959) Classification of this disease is difficult it appears to be essentially the same pattern as the other rheumatic diseases in which the delayed response affects the β-globulins at least as much as th γ-globulins (similar to bronchial asthma)

Rheumatic fever again produces the characteristic immediate and delayed response pattern previously observed by Sunderman and Sunderman (1957) Less significant changes were reported by Ogryzlo, Maclachlan, Dauphinee and Fletcher (1959) A solely delayed response pattern was found in chronic rheumatic heart disease in which, except for a marked γ-globulin elevation the protein distribution was normal. On the other hand the post infective arthropathies showed only an immediate response pattern with normal β- and γ-globulins.

Four cases of polymyositis revealed a slight albumin depletion, a very marked ncrease n α_1-globulins, a marked increase in α_2-globulins, and a slight increase in β-globulins. Whether this implies a pure immediate response pattern or a fused pattern as in Reiter's syndrome and bronchial asthma is difficult to say Patients with osteoarthritis possess a perfectly normal electrophoretic pattern as recorded by Jencks, Smith and Durrum (1956)

Two cases of disseminated lupus erythematosus revealed very marked hypoalbuminaemia, normal intermediate globlins, and very marked increases in γ-globulins. Ogryzlo Maclachlan, Dauphinee and Fletcher (1959) reported 48 /₆ of their 56 cases to have raised γ-globulins. Statistical evidence failed to confirm the γ-globulin suppressive action ascribed to steroids (Reiner 1950) although admittedly no pre-steroid values were available. The mean values of untreated and steroid-treated groups were similar

The case of polyarteritis nodosa showed moderate hypoalbuminaemia, marked elevation of α-globulins, normal β-globulins, and a very marked increase in γ-globulins. It is probably a fused pattern of immediate and delayed responses.

Table XXXII Distribution, in standard deviations from the normal mean, of serum protein fractions in rheumatoid arthritis

Fraction	Standard deviations from normal mean																			
	−7	−6	−5	−4	−3	−2	−1	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12	+13
A	2	1	6	7	6	2	1	—	—	—	—	—	—	—	—	—	—	—	—	—
α_1-G	—	—	—	—	1	—	—	1	3	4	4	3	3	1	3	1	1	—	—	—
α_2-G	—	—	—	—	—	1	2	1	1	4	2	6	4	1	1	1	1	—	—	—
β-G	—	—	—	—	—	—	1	3	7	7	3	—	—	1	—	—	1	—	—	—
γ-G	—	—	—	—	—	—	3	3	2	6	1	4	1	1	—	1	1	—	1	1
TG	—	—	—	—	—	—	—	1	1	4	4	2	5	3	—	1	—	2	—	2
TP	—	—	—	—	1	1	6	7	6	1	1	—		—	—	—	—	—	—	—

Mean value.

nation showed definite evidence of poly arteritis nodosa on the specimen received after appendicectomy The patient im proved on steroids

Results

Tables XXXI and XXXII indicate that serum protein changes in rheumatoid arthritis comprise a moderate decrease in albumin marked increases in the α-globulins a slight increase in β-globulins, and a moderate increase in γ-globulins The net result is hyperglobulinaemia and a normal total protein level. Essentially similar results have been described in the literature (Jencks, Smith and Durrum, 1956 Bonomo 1957 Sunderman and Sunderman, 1957 *Ogryzlo Maclachlan* Dauphinee and Fletcher 1959) Some of the authors regard these changes as non specific (Ogryzlo, Maclachlan, Dauphinee and Fletcher 1959) because of the variety of patterns obtained in this disease. The present study proves that the electrophoretic changes occurring in rheu matoid arthritis are a very sensitive index indeed of pathological activity Relatively *normal patterns* have always been associated with minimal disease activity Many previous authors failed to *indicate* the degree of activity present in their chronic rheumatoid arthritic cases.

In our opinion two types of protein distribution can be distinguished in rheu*matoid arthritis one is the characteristic* hypoalbuminaemia and elevated α-globulins (the immediate response pattern) while the second is characterized by elevated β- and γ-globulins (the delayed response pattern) There is no doubt that hyperglobulinaemia is fundamental to rheumatoid arthritis. The increased α-globulins occur in the active phase of the disease and are associated with inflammatory or exudative changes *(Layani* Bengul and De Mende, 1952 Olhagen 1952 Jacqueline, Traverse and Benson, 1954 Ropes, Perlmann Kaufmann and Bauer 1954) increased γ-globulins appear later with *the reactionary fibrous.* Sudworthy *Payne, Shetlar and Shetlar* (1957) In a careful selection of groups found that changes in α-globulins are *closely related to inflammatory activity* as the serum *protein bound* carbohydrate and both α-globulins increased with de terioration of disease. *Hypoalbuminaemia* developed with increasing severity of the disease. They found that the total serum *glycoprotein level exhibited the highest*

globulin, γ-macroglobulin α_1-mucoprotein, ceruloplasmin, prothrombin, and haptoglobins β-globulins include β_1-lipoproteins, lipid-poor euglobulins, transferrin, properdin β_1-globulin and β_2A globulin γ-globulins comprise γ_1-macroglobulin, 7S γ-globulins, and antibodies (Putnam, 1960)

The implication is that while the concentration of some entities may be selectively altered in certain disease states, their effect may be counterbalanced by the opposite effect of another component or dwarfed in generalized variation of many components. The technique is insensitive to the measurement of individual proteins and can only analyse the total conglomeration.

The present survey is an attempt to reinstate the quantitative electrophoretic analysis of serum proteins in its correct clinical milieu. From a careful assessment of the findings here, it is claimed that it provides the clinical biochemist with the most sensitive single laboratory estimation t help discriminate health from disease. It is known that the serum proteins remain constant within narrow limits in health with small variations due to sex, age, nutritional state, and genetic background. Hence every significant alteration in the normal pattern denotes an abnormal state in the body's protein pool. S ch abnormal protein states may be classified into two types, dysproteinaemia and paraproteinaemia. The former signifies a quantitative alteration of normal protein fractions while the latter term, invented by Apitz (1940) to describe the abnormal myeloma globulins, infers a qualitative and hence quantitative alteration. Such paraproteins are marked by the ppearance of a discrete spiked band in the α_2- to γ-globulin region of the electrophoretic strip

Dysproteinaemia may be further grouped into five types of pattern as judged by the response of the protein pool to disease.

Immediate Response Pattern This arises from tissue injury of many kinds and is the customary finding in the acute state. It consists of hypoalbuminaemia and elevation of both α-globulins. The correlation between albumin and the α-globulins was noted by Chow (1947) and ascribed to hepatic conversion of plasma albumin to a substance possessing the electrophoretic mobility of α-globulin as a response to many different types of stress or tissue necrosis (Roberts and White, 1949 Roberts and Kelley 1956) It is clear that simple caloric under nutrition does not explain this phenomenon (Taylor Mickelson and Keys, 1949) which has also been observed to arise from the increased catheptic activity of cancer sera (Libenson and Jena, 1957) It is noteworthy that in normal serum protein interrelations the most significant inverse correlation is that between albumin and α_1-globulin, suggesting that some α_1-globulin material may be a normal degradation product of albumin (Brackenridge, 1960)

Delayed Response Pattern. This is a hyperimmune type of reaction to injury and is a frequent finding in the chronic phase of tissue injury Marked by depletion of albumin and concomitant increase of γ-globulins, possibly coupled with elevated β-globulins, this effect stems from a generalized mobilization of antibodies which are not evident immediately like the α-globulins because of their longer turnover rate.

Depleted Response Pattern. This is characterized by a decrease in one or more fractions due to a reduction in concentration of one or more components of the

Since the *pioneering* electrophoretic studies of Tiselius (1937) many publications have appeared describing changes in human serum protein distributions. These were mainly undertaken in an attempt to aid diagnosis of various disorders. The early methods with their expensive apparatus and laborious techniques often failed to supply practical assistance to the clinician although they opened up a new research field for the protein chemist. With improved methodology however the temptation was great to produce disease-specific diagnostic tests. Such attempts were neither fruitful nor encouraging for most observed abnormalities fall into a small number of patterns which are usually characteristic of a whole group of pathological states. Wuhrmann and Wunderly (1954) introduced the term constellation to describe such patterns and listed nine of them. Within each constellation there are degrees of severity

In our observation every attempt to ascribe a specific protein distribution to a particular disease is logically and *physiologically* assailable. This can be understood by a theoretical consideration of the limitations of the material with which one deals (namely the protein pool) and the limitations of the technique which one uses (namely quantitative electrophoresis)

Limitation of material

It is unnecessary to emphasize the role played by proteins in the whole of the body However important and sensitive their function may be, it is unrealistic to anticipate a similar degree of specificity to external or internal traumatic *stimuli* to that expected from the total organism. Stated in logical language, a part cannot yield a response as specific as that of the system taken as a whole. Protein aberrations, according to this view must be examined in the light of the whole complex context of clinical and laboratory findings before any diagnostic or prognostic deductions can be drawn. No protein pattern may be deemed solely sufficient as a pathognomonic index. However to take the reverse situation, when associated with a definite disease state, the proteins will respond to the general nature of the state in a reliable and frequently characteristic manner

Limitation of technique

With the possible single exception of albumin each electrophoretic fraction consists of a heterogeneous array of proteins with varying physicochemical metabolic, and functional properties possessing similar *isoelectric points* In a qualitative sense, if the enzymes are logically included among the proteins, then each fraction must comprise thousands of different components. Quantitatively however only a small number are of *any* importance in normal serum Thus albumin includes a negligible concentration of the prealbumins α_1 globulins comprise mainly α_1-glycoprotein, α lipoproteins and thyroxine binding globulin α_2-globulins comprise mainly the unconjugated α_2-

Table XXVIII Diseases associated with various types of response pattern

Normal response pattern
- Benign neoplasia
- Primary carcinoma
- Psychopathic personality
- Neurosis
- Depression
- Schizophrenia
- Allergic dermatitis
- Neurodermatitis
- Psoriasis
- Follicular lymphoma
- Iron-deficiency anaemia
- Chronic peptic ulcer
- Crohn disease
- Thyrotoxicosis
- Uncomplicated diabetes
- Osteoarthritis

Immediate response pattern
- Acute bacterial infection
- Metastatic carcinoma
- Myocardial infarction
- Organic mental state
- Pancreatitis
- Cholecystitis
- Acute renal failure
- Urinary tract infection
- Polycythaemia vera
- Post-infectn arthropathy
- Polymyositis

Delayed response pattern
- Malaria
- Mycosis fungoides
- Pemphigus vulgaris
- Purpura hyperglobulinaemica
- Hepatic cirrhosis
- Acute hepatitis
- Chronic Rheumatic heart disease
- Disseminated lupus erythematosus

Augmented response pattern
- Angina pectoris
- Degenerative cardiovascular disease
- Cholelithiasis
- Ureteric calculi
- Obesity from overeating
- Hypercholesterolaemia
- Myxoedema
- Adrenogenital syndrome

Depleted response pattern
- Erythroleukaemia
- Addisonian anaemia
- Drug-induced haemolytic anaemia
- Haemophilia
- Malabsorption syndrome
- Chronic renal failure
- Alcoholism with malnutrition
- Anorexia nervosa
- Cachexia
- Acromegaly

Irregular response pattern
- Normal pregnancy
- Pre-eclamptic toxaemia
- Essential hypertension of pregnancy
- Nephrotic syndrome

Paraproteinaemic response pattern
- Myeloma
- Macroglobulinaemia
- Idiopathic paraproteinaemia

Mixed response patterns

Immediate and delayed
- Chronic infection
- Infectious mononucleosis
- Viral infection
- Sarcoidosis
- Bronchial asthma
- Exfoliative dermatitis
- Lymphosarcoma
- Reticulum cell sarcoma
- Hodgkin disease
- Hashimoto disease
- Rheumatoid arthritis
- Ankylosing spondylitis
- Reiter syndrome
- Rheumatic fever
- Polyarteritis nodosa

Immediate and augmented
- Degenerative cardiovascular disease with congestive cardiac failure
- Gout

Immediate and depleted
- Chronic myeloid leukaemia
- Myelofibrosis
- Acute hepatic necrosis
- Auto-immune anaemia
- Ulcerative colitis

Based on less than five cases.

fractions. The phenomenon occurs in deficient protein synthesis abnormally rapid catabolism and non metabolic protein destruction (such as hypohaptoglobinaemia arising from haemolysis or inefficient erythrocyte maturation)

Augmented Response Pattern. This is the reverse of the above type of pattern and may be due to excessive protein synthesis, abnormally slow catabolism, and deposition of material in the blood (such as hyperlipoproteinaemia in atherosclerosis)

Irregular Response Pattern At least two patterns do not appear to conform to or be explained by the principles of, the regular foregoing types of response. They occur in the nephrotic syndrome and in pregnancy Although not completely unique and hence not fully specific, they are nevertheless strongly presumptive of a particular disease. Thus the nephrotic pattern is observed in a few cases of leukaemia and a_1-myeloma, while mild forms of the pregnancy pattern have been found occasionally in steroid treated bronchial asthma. In essence it is probable that at least part of the irregularity stems from an organic alteration such as faulty glomerular filtration rather than a deranged physiological response to disease.

Paraproteinaemic Response Pattern. This differs from the previous five types in being essentially qualitative in its abnormal features.

In our opinion these are the six fundamental electrophoretic distributions representing an altered protein equilibrium occasioned by disease. Obviously mixtures of various patterns will be frequently encountered as a result of complications or phases existent in the disorder at the time of analysis. In every case, however resolution of pure patterns should be possible from the mixture.

It will be noted that the *serum protein* distribution cannot be expected to elucidate the aetiology of a disorder but furnishes an important tool among other laboratory tests to understand the natural history of a disease at various stages. The usefulness of serial in preference to single determinations is stressed in connection with response to treatment, progress of disease, and prognosis. Being a relatively inexpensive rapid, accurate, and reproducible method it is irreplaceable in the assessment of the biological response state at a point in the course of an illness. These characteristics provide the clinician with data of prognostic value and, in association with other relevant results of diagnostic assistance.

Table XXXIII summarizes the various diseases which make up the six types of response pattern Proper interpretation of an electrophoretic pattern must take into account the genetic background, age, and nutritional state of the patient before illness. Further the pattern should first be approached as a whole in order to determine its type of response before proceeding to estimate the severity of the disorder as reflected by the magnitudes of the fractions. It should be remembered that all conclusions have been based on average figures and that sometimes wide deviations from the mean are encountered.

The present study reveals that there are a number of disorders which fail to cause an upset in the normal physiological protein equilibrium. On the other hand, there is a wide range of disease states which, irrespective of their aetiologies, produce characteristic and often radical aberrations of the protein fractions.

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XVIII SUMMARY

Eight hundred and thirty cases of *infectious*, *neoplastic*, cardiovascular mental, asthmatic, dermatological haematological gastrointestinal, renal metabolic, obstetric, endocrine, hepatic, and rheumatic disorders have been selected in a survey of serum protein aberrations in disease.

Quantitative data provided by cellulose acetate electrophoresis have been assessed in the light of each patient's history with a view to studying the major types of response to pathological stimuli.

It is concluded that, while no electrophoretic distribution is reliably disease-specific, there are six general patterns which reflect the type of response of the patient at a particular time in the course of an illness Electrophoresis cannot inform on aetiology but is useful for diagnosis in association with clinical and other laboratory tests, for following the natural history of disease, for assessing response to treatment, and for prognosis. The disorders which give rise to the various types of pattern (immediate, delayed, depleted augmented, irregular and paraproteinaemic response) are listed.

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ACTA MEDICA
SCANDINAVICA

SUPPLEMENTUM 382

STUDIES ON THE CARDIOPULMONARY FUNCTION IN THE POST-INFECTIOUS PHASE OF "ATYPICAL" PNEUMONIA

By

HANS BERVEN

Accompanies Vol. 172

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CONTENTS

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INTRODUCTION

During the last two decades new and improved serologic methods and biological tests have led to a rapid growth of knowledge particularly as respects the etiologic problems of viral diseases. Systematic investigations of the cardiovascular function in these diseases have been carried out in recent years, both by histologic examination of the heart in fatal cases of virus infection, and by electrocardiographic studies during the course of the disease, and have brought much information about the involvement of the heart as well during the acute stage of illness as in the course following it. Thus, in series of followed-up patients, it has been shown that signs of myocarditis may persist for many years.

A pulmonary involvement in viral diseases of the respiratory tract has been demonstrated in series of autopsies in fatal cases of pneumonia. The histopathological lesions of the lung parenchyma were found to be of the same type as those observed in viral myocarditis. Consequently lesions of the lung parenchyma would be expected to persist a long time after the end of the acute stage of pneumonia. With the aid of now available routine tests of the pulmonary function, it would be possible to demonstrate physiological disturbances corresponding to such lesions, and thus, to obtain more information concerning their further evolution in this post-infectious stage. Results from a few investigations of the cardio-pulmonary function in the acute stage of viral or atypical pneumonia have been presented, but no systematic investigations of this function in the post-infectious stage seem to have been carried out.

The aim of the present investigation was to contribute to an increased knowledge of the possible disturbances of different components the cardio-pulmonary function in the course following the acute stage of "atypical" pneumonia, and to secure some information about the relation of changes in this function to the clinical or radiological findings during this stage.

CHAPTER I

Studies on the cardio-pulmonary function in the course following the acute stage of atypical pneumonia.

Introduction

The term "atypical" or virus pneumonia refers to an acute pulmonary infection that does not conform to the usual pattern of bacterial pneumonia either clinically pathologically radiologically or therapeutically. Clinically it may be difficult, even impossible, to establish the etiology in cases of "atypical" pneumonia and the diagnosis is often a source of great confusion to the clinician. With the aid of modern serologic and virus diagnostic methods it may however, be possible, to differentiate between different infectious agents of viral or other origin. Because lesions on x-rays in these disorders tend to be patchy and less dense than those seen in pneumococcal pneumonia, they came to be known as "atypical" pneumonias, which is unfortunate, as they in this sense only can be considered atypical. A more logical designation for these illnesses would be "acute interstitial pneumonitis" (50) term which at least would be based on the pathological changes observed to occur during these maladies. Since the term "atypical" pneumonia has been widely used in the literature, it is unlikely that a satisfactory change in terminology can be made until the exact etiology of these disorders may be established. Harding and Snyder (55) have presented different groups of possible etiological factors of the "atypical" pneumonia (Table 1). It may be pointed out that also pneumonias caused by bacteria such as H. influenza may be "atypical" in clinical sense, but usually the term "atypical" pneumonia refers to a pneumonia of viral origin. In cases, where the clinical suspicion of virus pneumonia can be verified serologically or by direct virus cultures, the term "atypical" pneumonia should be replaced by the specific etiological one, such as influenza A or B, adenovirus, psittacosis or ornithosis and Q fever.

Special interest has been directed to the pneumonia usually called "primary atypical pneumonia", which is considered to be of viral origin and associated with the demonstration of cold hemagglutinins or of agglutinins for the streptococcus MG in the sera of patients with the disease. Contemporary interest in this form of pneumonia arose from reports which appeared between 1930 and 1940. However, numerous reports of similar cases are to be found in various publications, which appeared during the past five or six decades. Thus, in reports by Armsmith (3) Gallagher (48) Bowen (29) Allen (1) Reimann (101) Smiley *et al.* (125) Reimann and Havens (102) and Longcope (84) the clinical manifestations of this disease are described. Extensive reviews of the earlier literature in this field

rell (77) and Berglund (21). Sterner further points out that the presence of leucocytosis with an increase of neutrophils need not in itself speak against a virus infection, since, according to several authors, P.A.P. is also associated with fairly high leucocyte counts. Furthermore, in bacterial pneumonia (bronchopneumonia) the white cell count can sometimes be normal (87).

Radiology

The radiological picture varies in the individual cases of virus pneumonia. There may be unilateral fan shaped infiltration of one of the lower lobes or dense hilar or perihilar shadows with radiating, mottled densities. In several cases an extensive miliary soft, nodular type of density in both lungs may be present, and the positive roentgen findings may last for several weeks, months, rendering differentiation from pulmonary tuberculosis difficult (18, 108).

Pathology

Characteristic histologic changes noted in the lungs of eight fatal cases of virus pneumonia have been reported by Parker, Joliffe and Finland (98). An alveolar exudate of mononuclear type, interstitial infiltration predominantly of plasma cells and swelling and proliferation of alveolar lining cells was found. A hyaline-like membrane within the alveoli was found in half the cases. The occurrence of hyaline like membranes within the alveoli has also been observed in fatal cases of influenza during the 1918 epidemic (52). In the material presented by Parker, *et al.* bacterial infection seemed to play a minor role except in two cases in which there was some abscess formation. The pathology of the lungs in nine cases of Asian influenzal pneumonitis was studied by Soto, *et al.* (126). Secondary bacterial invasion was not considered important. Death was thought to be due to interstitial inflammation in the alveolar walls with the formation of dense hyaline membranes (fig. 1).

Histo-pathological changes in poliomyelitis of a similar type have been observed by other workers. Thus, Saphir (116) reported interstitial pneumonitis in six of seventeen cases of poliomyelitis. Jurow and Dolgopol (65) found the same picture in 31 of 121 fatal cases of poliomyelitis or 25,6 % of the series. Nordenstam (95) has reported 23 cases of interstitial pneumonitis in 26 fatal cases of poliomyelitis during the last epidemic in Stockholm 1953. The interstitial infiltrations in these cases were mainly composed of lymphocytes and monocytes with very few polynuclears. The vessels of the alveolar walls showed excessive dilatation, often giving an erroneous impression of general thickening of the walls. Large amounts of erythrocytes, intra-alveolar as well as interstitial, occured frequently and in addition to the erythrocytes, the alveoli contained, and often seemed expanded by edema fluid. Unlike pulmonary edema in other diseases, there are however much fewer and smaller vacuoles due to air.

The pathology and pathologic anatomy of adenovirus infection has been studied in fatal cases by Kawai (67) and Kaufmann, *et al.* (66). The histologic lesions of the lungs were of interstitial type with thickening of alveolar septa.

The pathological anatomy of primary atypical pneumonia has not been investigated by many workers because the mortality rate of the disease is low. Golden (50) however had an unusual opportunity to record the morbid anatomy of this disorder in 4 cases in which the necropsy protocols and clinical histories were complete enough to warrant such a study. In this investigation all cases

have been presented by Dingle and Finland (37) McLeod (88) Owen (96) Schmitz (118) and Reimann (103)

It must be pointed out that it is difficult to find cases of pneumonia where it can be said with certainty that virus *alone* is operative (64) In a study of the etiology of respiratory infections in a series of 76 cases, made at the Epidemic Hospital Stockholm (46) it was shown that cases, serologically verified to be caused by different viruses, to a great extent were infected also by bacteria, and the series to be presented here probably does not differ from the above mentioned in this respect.

Clinic

Primary atypical pneumonia is characterized by fever headache cough and, in severe cases, other respiratory symptoms, such as dyspnea and/or cyanosis. After an incubation period of 7 to 21 days the following clinical picture is established. Initial complaints are fatique malaise, weakness, chills and headache. There is often pharyngitis, dry cough, chest pain and sometimes abdominal pain and vomiting Fever may be present for no longer than the first 48 hours, but can also last from a few days to several weeks

Physical signs in the chest are scarce or can be absent. The sputum, if present, usually does not contain the pathogens which are usually associated with bacterial pneumonias. The white cell count may be normal or low and the erythrocyte sedimentation rate is usually high. In an investigation of the clinical picture of primary atypical pneumonia (P A.P) in a material of 118 children, Sterner (130) found that white cell count varied from 2 000 to 21 000 with a normal or slightly increased number of neutrophils, and exceeded 12 000 in only five cases. A high sedimentation rate was a common feature which has also been found by Lan

Table 1 Possible Etiologic Agents for the Atypical Pneumonias

True Bacteria	Actinomycetales	True Fungi	Rickettsiae	Virus
Pasteurella tularensis, Hemophilus influenzae, and many other bacteria which are usually concerned in lobar & bronchopneumonia	Mycobacterium tuberculosis	Histoplasma capsulatum Coccidioides Blastomyces dermatitidis	Coxiella burnetii	Influenza viruses Lymphocytic choriomeningitis virus Mumps virus Measles virus Psittacosis-ornithosis group viruses Adenoviruses Primary atypical pneumonia virus or viruses? Coxsackie viruses ECHO viruses Hemadsorption viruses

Harding and Snyder AMA, Vol 1

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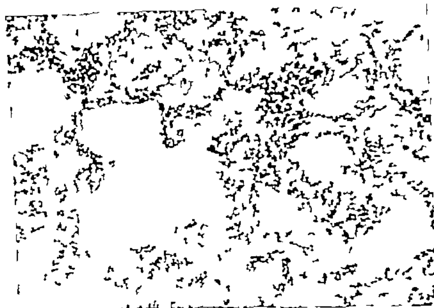


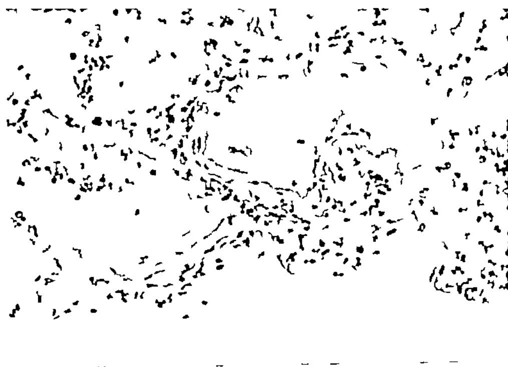
Fig 1 Interstitial pneumonitis in fatal case of "atypical" pneumonia. In the alveoli pronounced edema. General thickening of the interstitial tissue with massive infiltration of lymphocytes and monocytes. The interstitial infiltrations are often interwoven with intra-alveolar fibrinous exudate. The fibrin is often arranged as thin lamellas, giving an impression of membranes close to the walls of the alveoli. In large areas dense hyaline pleomorphic membrane-like formations, covering the walls of the alveoli, are also seen.
The pictures were obtained from the collection of *Dr H Nordenson* Pathological Institution, Serafimerlasarettet, Stockholm, and are published with his permission.

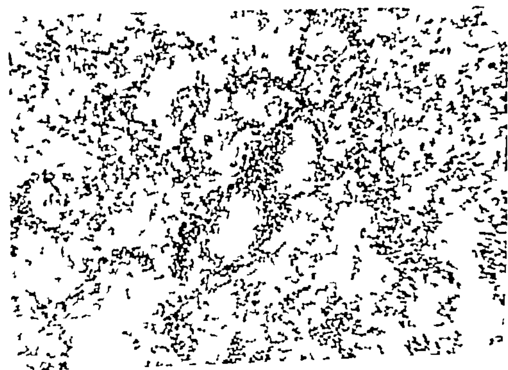
showed 1) Interstitial pneumonitis. 2) The alveoli either contained air or were collapsed, and they differed from those involved in bronchopneumonia and lobar pneumonia in being relatively free of polymorphonuclear leucocyte exudate.

Organization of the inflammatory process during the acute stage of pneumonia has been reported by numerous workers (5, 10, 30 52, 108, 114, 136)

Serology

In 1943 different serologic reactions were found to occur during the course of primary atypical pneumonia Two of these reactions have become useful in laboratory procedures which aid in establishing the diagnosis. Positive cold-hemagglutination reactions (99 132) and positive streptococcus MG agglutination reactions (133) thus were found in approximately 50 per cent of cases in which the diagnosis was made on clinical grounds. According to Feller (41) a titer of 1 32 or higher is suggestive of virus pneumonia (primary atypical pneumonia) Cold agglutinins appear at the end of the first week of illness and usually reach their maximum strength in two to four weeks. Feller states that high titers of 1 128 or 1 1024 or more are not often seen except in





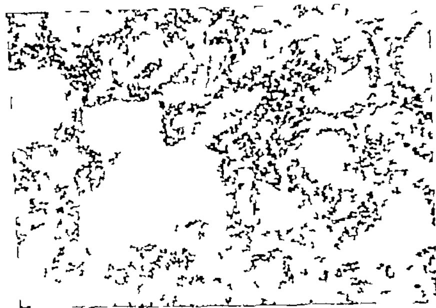


Fig. 1 Interstitial pneumonitis in fatal case of "atypical" pneumonia. In the alveoli pronounced edema. General thickening of the interstitial tissue with massive infiltration of lymphocytes and monocytes. The interstitial infiltrations are often interwoven with intra-alveolar fibrinous exudate. The fibrine is often arranged as thin lamellas, giving an impression of membranes close to the walls of the alveoli. In large areas dense hyaline pacdoophil membrane-like formations, covering the walls of the alveoli, are also seen.
The pictures were obtained from the collection of *Dr H. Nordenson*, Pathological Institution, Serafimerlasarettet, Stockholm, and are published with his permission.

showed 1) Interstitial pneumonitis. 2) The alveoli either contained air or were collapsed, and they differed from those involved in bronchopneumonia and lobar pneumonia in being relatively free of polymorphonuclear leucocyte exudate.

Organization of the inflammatory process during the acute stage of pneumonia has been reported by numerous workers (3, 10, 50, 52, 108, 114, 136).

Serology

In 1943 different serologic reactions were found to occur during the course of "primary atypical pneumonia". Two of these reactions have become useful in laboratory procedures which aid in establishing the diagnosis. Positive cold-hemagglutination reactions (99, 132) and positive streptococcus MG agglutination reactions (133) thus were found in approximately 50 per cent of cases in which the diagnosis was made on clinical grounds. According to Feller (41) a titer of 1:32 or higher is suggestive of virus pneumonia ("primary atypical pneumonia"). Cold agglutinins appear at the end of the first week of illness and usually reach their maximum strength in two to four weeks. Feller states that high titers of 1:128 or 1:10 4 or more are not often seen except in

primary atypical pneumonia A fourfold or greater increase in titer occurring during the course of the illness is significant, as is also a marked decrease in titer in the convalescent phase. This decrease must, however occur six to eight weeks after onset. An *increase of titer from negative to 1 16 in the* acute stage of the illness may also be regarded as positive according to Laurell (77)

Etiology

A number of viral and rickettsial diseases may present clinical pictures similar to or even identical with "primary atypical pneumonia The etiology of this disease is however still obscure, despite of very thorough investigations by a number of workers 1944, Eaton *et al* (40) reported the isolation of an agent from cases of P A.P Recently Liu and Coffin (83) have reported identifying cer*tain viral agents by indirect fluorescein anti*body tests They showed an antigenic relationship to the primary atypical pneumonia virus originally isolated by Eaton *et al*

Earlier Inestigations of the cardio-pulmonary function in pneumonia

Several investigations of the pathophysiology in the acute stage of *lobar* pneumonia have been presented Thus as early as 1919 Stadie (128) reported 33 cases with an arterial oxygen saturation lower than 80 per cent, from which only one recovered. Meakins and Davies (92) found that the carbon dioxide content of the arterial blood in lobar pneumonia was reduced on an average by about 15 per cent. The alkali reserve however was found to be normal or slightly reduced, the carbon dioxide dissociation curve not differing significantly from the normal From these findings it was concluded that a partially compensated alkalosis may exist, induced by the hyperventilation. *Similar results were presented by Hastings et al* (56) in studies of the blood reaction, blood gases and the acid-base balance in pneumonia. More recently Astrup and Harvald (9) studied the blood gases in 11 patients with pneumonia, of which 3 were virus pneumonias, in the acute stage of illness and in convalescense. In the acute phase *respiratory alkalosis and reduced arterial* oxygen saturation were observed. In the convalescense blood gases and oxygen saturation were within normal limits in all cases. In more severe cases of pneumonia, *however* acidosis due to retention of carbon dioxide has been found (109)

Venous admixture due to shunting of blood through affected parts of the lung in *the early stage of lobar pneumonia was sug*gested by Gross already 1919 (54) in a study on the permeability of the pulmonary vessels by intravascular injections post mortem. Rossier *et al* (112) found an appreciable *shunt to be present in one case of lobar* pneumonia. A decreased arterial carbon dioxide tension indicated hyperventilation of the functioning parts of the lung parenchyma

In bronchopneumonia, a higher degree of oxygen desaturation of the blood is usually present than in the lobar type The cyanosis may be extreme and explained by increased venous admixture due to shunt (25)

Impairment of oxygen diffusion was suggested, as early as 1922 by Schjerning (117) to be involved in the extreme cyanosis of influenza pneumonia. Kjerulf Jensen (74) found an approximately 40 per cent decrease in DL_{CO} as determined by $C^{14}O$ in one case of resolving pneumonia (infiltrations of upper left lobe) The results presented by McClement *et al* (89) *may also be men*tioned in connection with this. *They measur*

ed the oxygen diffusion capacity of the lungs in 10 patients with hematogenous tuberculosis with miliary distribution on x ray under treatment with streptomycin, and found it was reduced during the early acute phase, producing a pulmonary dysfunction similar to that in alveolo capillary block (11). The decrease in $D_{L_{O_2}}$ was considered to result from interference with gas diffusion produced by the exudates and acute inflammatory process in the alveoli at this stage of the disease.

From the results of the above mentioned investigations it seems to be possible to conclude that the hypoxia, frequently observed in acute pneumonia, is probably due to continued perfusion of the consolidated nonventilated lung (venous admixture) although a diffusion defect of varying degree may also be present (32).

However, no definite investigations of the cardio-pulmonary function in the course following bacterial and/or viral pneumonias, seem to have been presented to date.

The purpose of the present study

The patho-anatomical changes of the lung parenchyma described by different authors as typical in pneumonias caused by different viruses (and/or other etiologic agents) and the cardiopulmonary disturbances observed during the acute stage of illness, are of the nature that the author considers the following statements being justified:

1. If more or less extensive areas of the interstitial pneumonitis would undergo organization with the appearance of fibroblasts in the regional interstitial tissue of the lungs, i.e. the peribronchiolar tissue, alveolar walls and the pulmonary septa, a varying degree of impairment of the different pulmonary functions would be expected in the *course following* the acute stage of illness.

2. The process of diffusion across the alveolo-capillary membranes probably would be disturbed by changes of the thickness and/or permeability of these membranes or by decrease of the total diffusion area of the lungs. With the physiological methods now available it may be possible, to study not only the over-all diffusion capacity of the lungs, but also the membrane diffusion capacity and capillary blood volume.

3. Areas of affected parts of the lung parenchyma with alveoli still collapsed or closed and hereby non-ventilated in the post infectious stage, will probably cause an increase of the venous admixture.

The purpose of this study consequently is to investigate the cardio-pulmonary function with physiological methods available, and, if possible, to give an answer to the following questions:

1. Are the morphological changes of the lung tissue in the course following the acute stage of atypical pneumonias of such an order as to give demonstrable physiological disturbances?

2. To what an extent are such possible disturbances related to

a. The x ray picture at the time for investigation.

b. Signs and symptoms at the time for the investigation.

3. If impairment of the cardio-pulmonary function is shown to be present some weeks after the end of acute phase, to what an extent will this impairment be permanent?

The results of the planned cardio-pulmonary investigation in groups of patients with the clinical diagnosis of atypical" pneumonia will be presented and discussed in this and following chapters.

Material

A Atypical' pneumonia patients

16 cases aged 18 to 61 9 males and 7 females have been investigated at various times in the course following the acute infections. The material was selected with regard to the following criteria

1 *There should be no history of earlier* pneumonias or other pulmonary affections before the present illness.

2 This should, as far as possible, be verified by earlier normal x rays.

3 There should be no evidence of respiratory illness in the time interval from the end of acute pneumonia to the time of the investigation.

It is quite impossible clinically to ascertain the end of the acute infectious stage, as the disappearance of symptoms and normalisation of fever x ray picture sedimentation rate, etc. are not running parallel. To get a fairly uniform and comparable estimate of the above mentioned time interval it was decided in this material that the end of the acute stage was reached *four days* after normalization of body temperature

In order to make the clinical diagnosis of atypical pneumonia as accurate as possible, the following criteria were set up

I Major criteria

1a. Demonstration of a positive cold hemagglutination test A fourfold or greater increase in titer occurring during the course of the illness was regarded as significant as was a marked decrease in titer in the convalescent phase. This decrease must occur however six to eight weeks after onset. An increase of titer from negative to 1 16 in the acute stage of the illness was also regarded as positive according to Laurell (77)

1b Positive serologic reaction for any of the following viruses influenza, psittacosis, adenovirus. A fourfold or larger increase in titer was regarded as significant (18 68)

2 Negative effect of penicillin or sulfa treatment on fever The effect has been judged negative if fever remained unchanged *four days after antibiotic treatment* was started.

3 X ray picture in the acute stage diverging from that usually seen in bacterial pneumonias. In a comparable investigation of 33 cases with the clinical diagnosis of bronchopneumonia (own observations, unpublished) the diffuse nodular infiltrations, frequently seen in the present series, were found in only a few cases It must however be pointed out that this special type of diffuse nodular infiltration is *not* seen in all cases of virus pneumonia.

II Minor criteria

1 Clinical picture diverging from that usually seen in bacterial pneumonias. The *symptoms varied considerably depending on* the degree of distribution within the lung parenchyma. However in comparison with the 33 cases of bronchopneumonia it could be stated that 1) a *severe inproductive cough* seemed to occur more frequently in the present series, as well as 2) *myalgias* 3) *chills* and 4) *moderately severe headache* in the first few days of the acute stage. Localized stitch or pain in the thorax frequently occurring in the bronchopneumonia group, did not seem to be a pronounced symptom in the present series.

A high sedimentation rate and ordinary low white cell count as minor criteria for the atypical pneumonia were not valid, as the comparative investigation of the bronchopneumonia group showed that almost half

of the cases in this group had sedimentation rates greater than 50 and white cell counts less than 10.000.

Negative bacteriologic naso-pharynx and sputum cultures seem to be of little value as a minor criterium either with or without preceding antibiotic treatment, which was given in all but 3 cases in the actual group.

A positive or probably positive cold hemagglutination or other likewise positive or probably positive virus antibody test was found in 13 cases and it may thus be stated with some degree of probability that the atypical pneumonia at least primarily seems to have been of the virus type in these cases. *Most of these cases also meet the* other two major criteria and several of the minor ones, which seems to increase the probability for the clinical diagnosis of virus pneumonia.

Of the remaining 3 cases (nos. 6, 7 and 10) case no 6 satisfies two major criteria (other than positive serologic reaction) and all minor criteria. Case no. 7 meets one major and one minor criterium, why cer tain probability for the clinical diagnosis may be said to be present. Case no. 10 does not meet any major but three minor criteria, and the clinical diagnosis therefore is rather uncertain, but has been included in the material, as, on the other side, nothing *speaks in favour of a bacterial pneumonia.*

Fig. 6 illustrates the frequency of these clinical data, which have been chosen as major or minor criteria, in the atypical pneumonia group in comparison to the bronchopneumonia group (personal observa tions, unpublished)

The interval from the end of acute infec tion to the time of investigation was in cases nos. 1—4 4—27 months (table II) depending on the fact that, before the investigation started, all cases with the clinical diagnosis of atypical" pneumonias nursed in the Epidemic Hospital during about two years preceding t, were examined with regard to the suitability for the present study and then these four cases were found to meet with the above mentioned criteria better than the others.

The other 12 cases have been taken to the investigation as soon as possible after the end of the acute infection with some what varying time intervals due to the pa tient's clinical status, regression of x ray changes, and other practical circumstances (stay in convalescent institutions etc.)

Many cases of the atypical pneumonia group have in the course *following* acute infection suffered from more or less pronounced symptoms such as fatigue, cough and dyspnea on exercise (see *table II*) The duration of these symptoms has varied widely from a few weeks to several months.

B Control material

12 cases, in convalescence after non-pulmonary diseases, aged 20—60, 12 males and one female, have, in order to find out if convalescense *per se* could have any influence on the cardio-pulmonary function, been investigated in the same way The pa tients have to a large extent been convale scents after acute infections usually not in volving the lungs (table III) There was no history of earlier pneumonias or other pul monary affections and this is mostly verified by earlier x-ray controls. Most cases were investigated while still remaining in the *hospital, having left bed at least* one week earlier. By using convalescents of non-pulmonary disease and not healthy normals in comparison to *convalescents of* pneumonias, it was thought possible to eliminate,

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Many cases of the "atypical" pneumonia group have in the course following acute infection suffered from more or less pronounced symptoms such as fatigue, cough and dyspnea on exercise (see table II). The duration of these symptoms has varied widely from a few weeks to several months.

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Table II Case reports in 16 patients with "atypical" pneumonia.

[illegible]	Case	Sex	Age	Earlier known respiratory infection	Earlier X-ray controls of the lungs	Duration of fever (days) in the acute phase of illness	Antibiotics used in acute phase	Effect of treatment on fever (1)	Symptoms during acute phase of infection: Chills	Headache	Severe unproductive cough	Myalgia	Sore throat	Anorexia	Fatigue	Other symptoms	Labora[tory]: ESR highest
pn. atyp [illegible]	1	M	27		Normal		no	uncertain			(+)	(+)				Meningism	64
pn. atyp	2	M	54	Bronchitis	1948 normal	1	no	no		(+)							164
[illegible] pn.		M	33		Calcified [illegible] left lung with small calcification left lower lobe	33	no Chloromycetin	uncertain								Dyspnoea slight cyanosis	11
pn. atyp.		M			1950 normal	22	Aureomycin	no	(+)							Slight cyanosis	42
pn. [illegible]		M	1		[illegible] emphysema in right upper lobe	12	no	no	(+)							Slight dyspnoea	114
pn.		M	66		Normal	23	no Streptomycin	no		++		++				Cyanosis dyspnoea	94
[illegible]	7	F	22	–	Aug. 1948 normal								(+)				53
pn. atyp.		M	47		Calcified lymphnode in right hilus	2½	no Chloromycetin	no	(+)			(+)				Slight cyanosis dyspnoea	1
[illegible]	9	M	16		1948 normal	1		uncertain		(+)		(+)	(+)				26
[illegible] virus-	10	M	68		1948 normal								(+)				73
pn. atyp.	11		66		1948 normal	30	no	no	(+)	(+)		(+)				Dyspnoea cyanosis	135
pn. atyp.	12	F	21	Influenza 1948, no signs of pneumonia	1948 normal	12			(+)				(+)		(+)		76
pn. atyp	13	F	30		1950 Small calcification right upper lobe	30	no Streptomycin	uncertain									60
pn. atyp.		F	36		1948 normal	1	no	no	(+)				(+)			Cyanosis	93
pn. atyp.	15	F	46		1947 normal		no	no				(?)				Slight dyspnoea	67
pn. atyp.	16	F	31		1947 normal		no.	no	(				(+)				3[illegible]

(1) [Nor]malisation of body temperature within four days
[illegible] of acute stage is here defined as [illegible] days after normalisation of body temp.

Acute phase of illness									X-ray lesions acute phase	X-ray lesions at the last examination	Resp. symptoms in convalescence			Time from end of acute phase to last examination
Throat flora	Sputum bacterial cultures		Cold hemagglutinin titer		Influenza C-F titers		Other viral C-F titers				Fever	Cough	Shortness of breath during [illegible]	
not pre-treated	without pretreatment	with pre-treated	serum I	serum II	serum I	serum II	serum I	serum II						
			1/32	1/128					Extensive infiltration and diffuse nodular areas within the whole right lung	Total regression				
Common flora		No growth	1/64	1/16					Diffuse nodular areas within both lungs	Total regression		(+)	(+)	1?
Common flora		Auto-flora		1/16					Extensive infiltration and diffuse nodular areas both lungs	Total regression		(+)	(+)	2?
Common flora		No growth	1/32	1/64					Diffuse nodular areas both lungs	Total regression		(+)		2?
Common flora		[illegible]			[illegible]	[illegible]			Diffuse nodular areas both lungs	Total regression		(+)		1
		[illegible]			[illegible]	[illegible] neg			Diffuse nodular areas in both lungs to great extent [illegible]	Practically total regression	(+)			1/2
[illegible]	No growth				[illegible]	[illegible]	Adeno [illegible] [illegible]	[illegible]	Diffuse nodular areas in both lungs	Total regression		(+)		1/2
Common flora		Common flora	1/64	1/512					Diffuse nodular areas both lungs	Total regression		(+)		1/2
Common flora		Common flora					Adeno 1/512 [illegible] neg Q fever neg	1/? neg neg	Confluent nodular [illegible] the lower lobes of both lungs	Total regression				1/2
[illegible]	No growth				[illegible] neg	neg	Adeno		Diffuse [illegible] the base of the right lung	Total regression	(+)		(+)	1/2
Common flora			1/512	1/256					Diffuse nodular areas both lungs	Total regression		(+)	(+)	1/2
[illegible]	Moderate number of [illegible]		1/64	1/		[illegible]	Adeno neg		Diffuse [illegible] and nodular areas in both lungs	Total regression		(+)	(+)	1/
Common flora		Common flora	neg	1/256					Massive [illegible] left lung and [illegible] in the right lower lobe	[illegible] regression				
Common flora		Common flora	1/2	1/512					Massive infiltration and diffuse nodular areas both lungs [illegible] right lung	Total regression		(+)	(+)	1/2
			1/64	1/1024					Diffuse nodular areas both lungs	Total regression		(+)		1/2
Common flora		Common flora	neg	1/64					Confluent [illegible] the right middle lobe and the basal parts of the right lower lobe	Total regression		(+)		1/

Table II Case reports in 16 patients with "atypical" pneumonia

Clinical Diagnosis	Case	Sex	Age	Earlier known respiratory infection	Earlier X ray contrasts of the lungs	Duration of fever (days) in the acute stage 2)	Antibiotics used in acute phase	Effect of treatment on fever 1)	Symptoms during acute phase of infection: Chills	Headache	Severe cough	Myalgia	Sore throat	Anorexia	Fatigue	Other symptoms	Labor... SR, highest in
Pn. prim atyp meningitis serosa		M	37		Normal		no	uncertain			(+)	(+)				Meningism	64
Pn. prim atyp.	2	M	56	Bronchitis	1956: normal	1	no	no		(+)							160
Infl? Br pn.	3	M	63		Calcified stripes left lung with small calcification left lower lobe	25	no Chloromycetin	uncertain								Dyspnoea slight cyanosis	11
Pn. prim atyp.		M	44		1956 normal	23	Aureomycin	no	(+)							Slight cyanosis	103
Infl e. pn. bilat nephritis ac		M	61		Prior bi- Bullous emphysema in right upper lobe	12	no	no	(+)							Slight dyspnoea	
Infl e. pn bilat.		M	60		Normal	25	no Streptomycin	no		++		++				Cyanosis dyspnoea	94
Pn. ac interstitialis		F	22	—	Aug. 1960 normal								(+)				83
Pn. prim atyp.		M	47		Calcified lymphoma in right hilus	24	no Chloromycetin	no	(+)			(+)				Slight cyanosis dyspnoea	1
Pn. atypica adenovirosis?		M	18		1960 normal	16		uncertain		(+)		(+)	(+)				30
Pn. dx (virus-inf.)		M	63		1956 normal								(+)				73
Pn. prim atyp.	1	F	60		1960 normal	20	no	no	(+)	(+)		(+)				Dyspnoea cyanosis	123
Pn. prim atyp.	12	F	21	Influenza 1960 No signs of pneumonia	1960 normal	13			(+)				(+)		(+)		78
Pn. prim atyp	13	F	30		1956 Small calcification right upper lobe	26	Pc. Streptomycin	uncertain									104
Pn. prim atyp.	4	F	20		1960 normal	1	no	no	(+)				(+)			Cyanosis	68
Pn prim atyp	5	F	40		1957 normal	1	pc.	no				(+)				Slight cyanosis	87
Pn. prim atyp.		F	21		1957 normal		pc.	no	(				(+)				29

1) Normal values of body temperature within four days

2) End of acute stage is here defined as days after normalisation of body temp









Fig. 3. Case 2, acute stage of pneumonia. Diffuse nodular areas within both lungs.

b. At the time of investigation. Total regression of parenchymal infiltrations.

both at rest in supine position, standing, during exercise in sitting position and after work in supine position. During work the indifferent electrode was placed on the forehead (CH) (124) and only precordial leads were taken. Following chest leads were recorded: CH_2, CH_4, CH_5 and CH_7. The ECG's were recorded with a 4-channel direct-writing apparatus. (Mingograph 42, Elema, Sweden.)

Physical working capacity (W_{170}). The orthostatic test was followed by a work test (122, 123, 134) on an electrically braked bicycle ergometer (59) in the sitting position. ECG was recorded every second minute of each work load, which lasted for 6

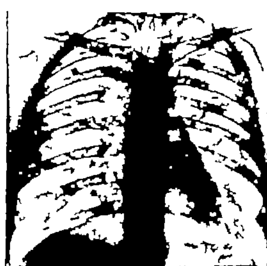





Fig. 2 a. Case 1 acut stage of pneumonia. Massive infiltrations and diffuse nodular areas within the whole right lung.

b. At the time of investigation. Total regression of the parenchymal infiltrations.

to a certain degree, such changes of the pulmonary function as might be induced by inactivity.

No significant differences according to the way of living, habits of smoking etc. have been found in the two groups.

Methods

Orthostatic test. Pulse frequency and EGG were registered after 8 minutes standing, the patient leaning the back of his head against the wall.

Electrocardiogram. ECG was recorded



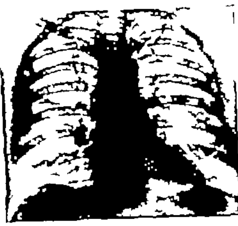






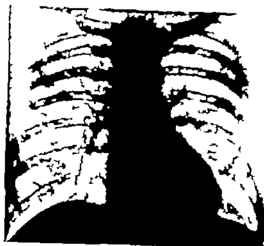
Fig. 5. Case 8, acute stage of pneumonia. Diffuse nodular areas in both lungs.

b. At the time of investigation. Total regression of parenchymal infiltrations.

mately linear relationship between pulse rate and work load (69, 70, 71).

Heart volume. The heart volume was determined in prone position by two-plane roentgenogram (76) irrespective of heart phase.

Spirometry. Spirometry with determination of the functional residual capacity and residual volume was performed with the helium dilution method using a katharometer for helium determination (58). The volume of the spirometer system with the bell in bottom position (V_O) was estimated to be 2323 plus or minus 24 ml BTPS, S.D.



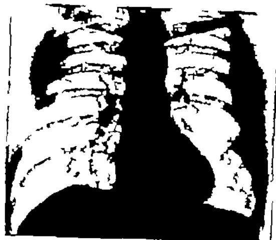




Fig. 4 a Case 3 acute stage of pneumonia. Massive infiltration and diffuse nodular areas in both lungs.



b At the time of investigation. Total regression of parenchymal infiltrations

minutes and the respiratory frequency counted in the middle of each load. The *physical working capacity* (W_{170}) *is defined* as the rate of work performed at a pulse rate of 170 beats/min. and in an approximate steady state i.e. 10 beats/min. or less change of pulse rate from second to sixth minute of work. By increasing the load every sixth minute (e.g. *300—600—900 kpm/min. for men and 200—400—600 kpm/* min. for women) it was attempted to reach a pulse rate of at least 150 beats/min. The value for W_{170} could then be obtained by graphical extrapolation using the approxi



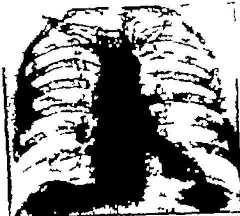






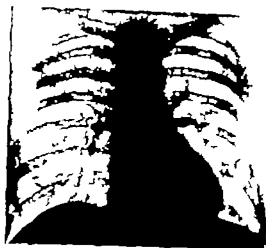
Fig. 5 Case 8, acute stage of pneumonia. Diffuse nodular areas in both lungs

b At the time of investigation. Total regression of parenchymal infiltrations

mately linear relationship between pulse rate and work load (69, 70, 71).

Heart volume. The heart volume was determined in prone position by two-plane roentgenogram (76) irrespective of heart phase.

Spirometry. Spirometry with determination of the functional residual capacity and residual volume was performed with the helium dilution method using katharometer for helium determination (58). The volume of the spirometer system with the bell in bottom position (V_0) was estimated to be 2323 plus or minus 24 ml BTPS, S.D.



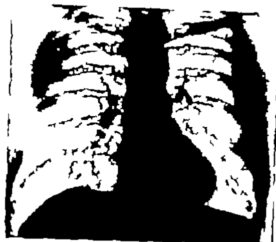






Fig. 4. Case 3: acute stage of pneumonia. Massive infiltration and diffuse nodular areas in both lungs.

b. At the time of investigation. Total regression of parenchymal infiltrations.

minutes, and the respiratory frequency counted in the middle of each load. The *physical working capacity* (W_{170}) *is defined* as the rate of work performed at a pulse rate of 170 beats/min. and in an approximate steady state, i.e. 10 beats/min. or less change of pulse rate from second to sixth minute of work. By increasing the load every sixth minute (e.g. *300—600—900 kpm/min. for men and 200—400—600* kpm/min. for women) it was attempted to reach a pulse rate of at least 150 beats/min. The value for W_{170} could then be obtained by graphical extrapolation using the approxi-

could during a period of 15 seconds with breathing frequency of his own. The test was repeated several times in order to get the subject familiar with the technique. Finally this test was modified in that way that the subject had to blow in the same way in the spirometer but with fixed breathing frequencies of 40 60 or 80/min. (MVV 40—60—80)

Analyses of the forced expiratory spirogram was made according to Lenallen and Fowler (78) All volumes were corrected to BTPS.

Normal values for these components of the forced expiratory spirogram were predicted from the equations used in this laboratory (53 73)

Nitrogen Wash-out N_2-wash-out curves were obtained, using essentially the technique described by Svanberg (131) and others (27) Nitrogen concentration was continuously analysed by a Lilly nitrogen meter as modified by Lundin and Akesson (85 86) The gas mixture to be analysed is drawn from the expiratory side of a three-way valve connected to the subject through a needle valve. With an Edwards Speedivac two stage pump and the pressure of 2 mm Hg, about 20 ml gas per minute is drawn through the instrument with a time lag of about 0.02 sec. for the gas sample to pass from the needle valve to the ionization tube, with a tubing of 2 meters length and an inner diameter of 2.5 mm. An Easterline Angus ink writer (0.2 sec. for full deflection) is used for direct reading with an accuracy of 1 per cent. On the inspiratory side of the three way valve was another valve, allowing the subject to breathe either air or pure oxygen. In the oxygen circuit is demand-valve,

Table III Some clinical data on 12 subject in the control series of non p lmonary d ease

Case no.	Sex Age	Clinical diagnosis	Earlier known lung diseases	Earlier x-ray control of the lungs	X-ray during acute stage of illness	X-ray at the time of investigation	Time from end of acute stage of illness, weeks*)
	33	[illegible]		Normal	Normal	Normal	
	26	Colitis ulcerosa		Normal	Normal	Normal	[illegible]**)
	34	Cephalalgia		Normal	Normal	Normal	[illegible]
	47	Salmonella [illegible]			Normal	Normal	[illegible]
	22	[illegible]		Normal	Practically normal	Normal	
	24	Salmonella [illegible]		Normal	Normal	Normal	
	60	Salmonella [illegible]		Normal		Normal	
		Angina [illegible]		Normal		Normal	
	[illegible]	[illegible]		Normal	Normal	Normal	
10		[illegible]		Normal	Normal	Normal	
	[illegible]	Salmonella [illegible]		Normal		Normal	[illegible]
12		[illegible]		Normal		Normal	

[illegible]
[illegible]

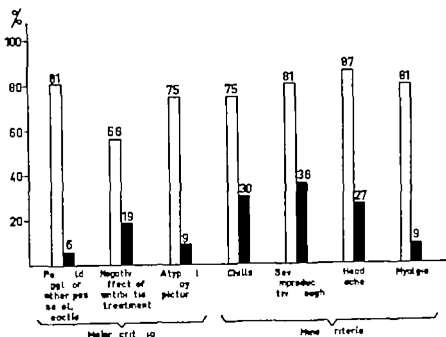


Fig 6 Some clinical data in the typical pneumonia group (n=16) compared with corresponding data for a series (n=33) of patients with bronchopneumonia. (Unpublished) For further explanation see text.

= 105 ml BTPS (n = 20) This can be taken as the error of the katharometer and spirometer The total error involved (= error of the katharometer spirometer and subject) has been determined from 7 duplicate determinations of functional residual capacity in 7 normals. The standard deviation of a single determination was calculated to be plus or minus 89 ml. BTPS, which agrees well with the results of Holmgren (58) and others (30 49 93)

Normal values for the static lung volumes were predicted from the formulae reported by Grimby and Söderholm (53) These normal values have been obtained with the same technique as in the present investigation.

Analysis of forced expiratory spirograms Determination of Maximal Breathing Capacity (MBC) (39) forced vital capacity (FVC) (24) forced expiratory volume in one second (FEV 1 0) (47) and maximal ex and inspiratory flow (MMF MMIF) (78) was performed on a modified Bernstein Spirometer[1] (23) The subject was sitting in the front of the spirometer breathing into it through a rubber mask slightly pressed against his face to avoid leakage. The subject was asked to make a maximal inspiration. At the end of this the kymograph was put on its highest speed (3 000 mm/sec.) and the subject was ordered to expire as fastly and deeply as possible and then, when the curve had reached its lowest, horizontal niveau, to make a forced maximal inspiration. The test was repeated several times with one or two minutes interval until the subject seemed to have performed as good curves as possible. For determination of MBC the subject was instructed to blow in the spirometer as fastly and as deeply as he

[1] Built by Lundia, Lund, Sweden.

volume to the functional residual capacity It was shown by Donevan *et al* that there is no evidence of any consistent change in the level of midcapacity as between rest and exercise and between different age groups at similar exercise levels. Consequently in comparison of D_{LCO} between individuals it may be suitable to correlate it to the midcapacity

Venous admixture Unsaturation of arterial blood caused by venous admixture due to shunt was determined according to Berggren (20) the subject breathing 100 % oxygen for 20 minutes in the supine position (15) Hereby other causes of unsaturation of arterial blood, such as uneven ventilation/perfusion and/or disturbances of diffusion, are eliminated (12, 15) If P_{O_2} is more then 150 mm Hg, the shunt is calculated according to the following equation

$$\frac{Q_A}{Q_T} = \frac{C_{\bar{c}O_2} - C_{aO_2}}{C_{\bar{c}O_2} - C_{\bar{v}O_2}} \qquad (1)$$

The approximate a—v O_2-difference was taken from the relation between a—v O_2 difference and pulse frequency published by Holmgren *et al* (61)

Normal values for venous admixture are reported to be below 3 2 per cent of the cardiac output (12, 13 15)

Analytical methods

Expired gas was collected in Douglas bags and gas volumes were measured with a gasometer (Nordgas) The reproducibility of readings on the gasometer was determined to be within ± 3 %.

Gas analy O_2 and CO_2 concentrations were determined with Haldane or micro-Scholander apparatus (119)

The error of method, expressed as the standard error of a single determination and checked at several occasions during the period of investigation from series of duplicate analyses (n = 20) was in both methods estimated to vary between 0.012 and 0.023 vol. %.

Carbon dioxide tension of arterial blood (P_{CO_2}) was obtained from pH measurements in the blood sample before and after equilibration with two CO_2 mixtures of known composition according to Astrup, using the Radiometer micro equipment (2) From duplicate pH measurements (n = 28) the error of single pH determination in this laboratory was found to be 0.0015 (coefficient of variation = 2 %) which is in agreement with the results published by Astrup (8) It is a little more difficult to state the error of the P_{CO_2} determinations, as it depends on the log P_{CO_2}/pH curve as well as the value of the actual P_{CO_2} as compared with the P_{CO_2} at which the equilibration takes place. If the P_{CO_2} is between the two reference tensions, the error will be approximately plus or minus 0 5 % If it is outside, within plus or minus 3 % (137) For calculation of the standard bicarbonate the nomogram by Astrup was used. All pH measurements were performed immediately after withdrawing the blood to eliminate the error by glycolysis.

Oxygen Tension of Arterial Blood (P_{O_2}) was determined with the polarographic method using the Clark electrode (33) with a polyethylene membrane. A null balance transistor amplifier and indicator used was built according to the circuit diagram published by Severinghaus and Bradley (121) with only minor modifications (91) The accuracy of the meter was 0.1 per cent of full scale.

Cuvette design The cuvette used was

type AGA divator universal, which regulates the pressure to about 5 atö in the inspiratory system, allowing the subject to inspire the required volume of oxygen for 7 minutes, during which period the nitrogen wash-out curve was registered on the inkwriter and the expiratory air was collected in a Douglas bag The nitrogen concentration in the ex pired air was then analyzed in the nitrogen meter and the expired volume measured in a gas meter (Nordgas) From the data so obtained the following calculations were made

1 The *nitrogen wash-out time* (the time from the beginning of oxygen breathing until the end tidal nitrogen concentration had reached 2 %) (27)

2 *Becklake's index (17) or intrapulmonary mixing index* =

$$\text{mixing index} = \frac{\text{volume of oxygen used to reach } 2\ \%\ N_2}{\text{FRC}}$$

3 Functional residual capacity (FRC) which was determined as the N_2-space that had been washed out at $F_{E_{N_2}} = 2\ \%$

The wash-out index could be determined with a reproducibility of 20 % which is in close agreement with that reported by others (17 63) Becklake suggests that indices more than 10 4 would be likely to indicate impairment of intrapulmonary mixing The N_2 wash-out time was determined with a reproducibility of 14 % Normal range has been reported to be 2 2—3 5 minutes and values above 4 minutes are regarded as pathological (27) FRC was determined with a reproducibility of 10 %

Four cases were studied with the single breath nitrogen elimination test, using essentially the technique described by Comroe and Fowler (35) Kjellmer Sandqvist and Berglund (72) and Sandqvist and Kjellmer (115) Expired volume and flow rate were measured by spirometer with a rotational transducer

Nitrogen concentrations and expired volume were recorded on a direct writing ink jet oscillograph (Mingograph, Elema) Analyses of the obtained single breath nitrogen elimination curves were made according to Kjellmer *et al* (72)

The diffusion capacity for carbon monoxide ($D_{L_{CO}}$) $D_{L_{CO}}$ was measured by means of the steady state CO method (43) with the modification that correction was made for the partial pressure of CO in the pulmonary capillary blood (81)

The CO air mixture containing 0 05 % CO was inspired from a Douglas bag and expired gas was collected in another Douglas bag

The measurement of $D_{L_{CO}}$ during work was performed on a bicycle ergometer (59) and the load was chosen to give a pulse frequency of about 140 beats/minute (81 82) Af er ₄ minutes of work the inhalation of CO-air mixture was started and after another 2 minute period the collection of expired air was started From a catheter introduced into the brachial artery (22, 120) arterial blood was withdrawn in the middle of the gas collection period for determination of P_{CO_2} and P_{CO} $P_{A_{CO_2}}$ was taken to be equal to P_{CO_2} which is approximately true when the venous admixture to arterial blood

$\left(\frac{Q_{s}}{Q_{T}}\right)$ is less than 0 15 (104 111)

Normal values of $D_{L_{CO}}$ in relation to age and oxygen consumption were predicted according to Donevan *et al* (38) Normal values of $D_{L_{CO}}$/m² BSA and $D_{L_{CO}}$/mid-capacity were predicted according to the same authors

The midcapacity of the lungs was calculated by addin, half the measured tidal

volume to the functional residual capacity it was shown by Donevan *et al.*, that there is no evidence of any consistent change in the level of midcapacity as between rest and exercise and between different age groups at similar exercise levels. Consequently in comparison of $D_{L_{CO}}$ between individuals it may be suitable to correlate it to the mid-capacity.

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$$\frac{Q_s}{Q_T} = \frac{C_{c'O_2} - C_{aO_2}}{C_{aO_2} - C_{\bar{v}O_2}} \qquad (1)$$

The approximate a—v O_2-difference was taken from the relation between a—v O_2-difference and pulse frequency published by Holmgren *et al.* (61).

Normal values for venous admixture are reported to be below 5.2 per cent of the cardiac output (12, 13, 15).

Analytical method

Expired gas was collected in Douglas bags and gas volumes were measured with a gasometer (Nordgas). The reproducibility of readings on the gasometer was determined to be within ± 5 %.

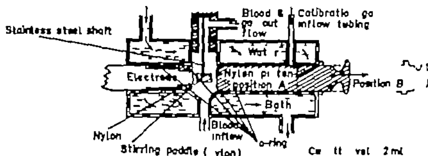
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Cuvette design. The cuvette used was



F g 7 Cuvette for oxygen electrode, according to Pitzele showi g method of sealing a stirring paddle and shaft into the analysis chamber For further explanation see text

made of pyrex glass and is a modification f the Severinghaus devise (100) (*Fig. 7*) With the piston in position A, the chamber is filled slowly from below while the stirrer is stationary The first ml. of blood, which is used to wash through the cuvette to stable P_{O_2} and dislodge any bubbles on the walls of the chamber is pushed out through the outflow tubing The stirrer is then turned on (stirring rate about 400/min.) and reading is made on the null balance meter the zero oxygen point of which is calibrated with pure tank nitrogen When piston is in position B the chamber is functioning as tonometer the humified gas of known P_{O_2} being bubbled through the blood for about 15 minutes from a thin catheter pushed in the calibration gas inflow tubing. The piston is then pushed in position A, the stirrer is turned on and reading is made Since electrode responses are linearly related to oxygen tension over the range to 1 atmosphere, this allows calibration with only one known gas (121) This reading is divided into that of the corresponding gas and the readings on the blood samples are multiplied by this ratio

Error of the method The accuracy of the P_{O_2} determinations according to this method will depend on following criteria

1 Constant temperature to plus or minus 0 1° C. 2. Constant rapid stirring of the liquid at the electrode surface. 3 Constant pressure in the cuvette. 4. No loss or gain of oxygen from the walls of the cuvette, or from openings, or conducting tubing 5 Choice of a suitable membrane. 6. Accurate equilibration of blood with known calibration gases of high or low tensions.

Number 1—5 have been met as far as possible by careful following of the directions recommended by Severinghaus (121) Number 6 was studied in the following way A blood sample was equilibrated with a high calibration gas (93 10 % O_2) 10 times (using the same membrane) and the P_{O_2} of the equilibrated blood was read on the polarograph each time. The variation coefficient was 1 93 % The same test was made with a low calibration gas (20 93 % O_2) giving a variation coefficient of 2.72 % The reproducibility of tonometry thus seems to be satisfying

The error of a single determination of P_{O_2} at high range of oxygen tensions (500—700 mm Hg) was estimated from duplicate readings on equilibrated blood to be 1 0 % (n = 9) In the low range (O_2 tensions 60—100 mm Hg) the error was estimated to be 1 4 % (n = 9)

Hemoglobin concentration (Hb conc.) mg/100 ml was determined spectrophoto-

metrically as reported earlier (60 129) The error of a single determination in this laboratory calculated from duplicate determinations was 0.53 per cent ($n = 50$) Oxygen capacity of the blood samples was calculated from the Hb conc. using 1 34 for the oxygen combining power of hemoglobin.

Carbon monoxide content of arterial blood (C_{CO}) was determined with a hopcalite apparatus (Stiller) after release of CO with $KH(JO_3)_2$ in an extraction chamber (80) The per cent CO-saturation S_{CO} was calculated from CO-content and hemoglobin concentration measured photospectrometrically using 1 34 for the carbon monoxide combining power of hemoglobin. Mean capillary CO tension ($\bar{P}_{cCO}$) mm Hg was calculated from S_{CO} according to Linderholm (81)

Statistics

In the present investigation conventional statistical methods have been used The significance of differences between groups was tested by the t-test. Most methods of calculation were taken from Snedecor (126) The degree of probability was designated as follows

*	$0.05 > p > 0.01$	probably significant.
	$0.01 > p > 0.001$	significant.
	$0.001 \geq p$	highly significant.

Result

Circulatory studies

Electrocardiogram ECG at rest was in the non-pulmonary group within the normal variation in 11 cases. In one (*case no. 3*) a slight ST and T deviation was observed, which was somewhat more marked in standing One case (*no. 12*) showed moderate deviation of ST and T in standing, probably of the sympathicotonic type (61b) During and after the work test the ECG was normal in all patients.

In the atypical pneumonia group ECG was within normal variation in all cases at rest. In 2 cases (nos. 12 and 14) marked ST and T deviation was observed in standing. During and after the work test ECG was normal in all cases.

Heart volume in prone position was on an average 737 5 ml in the non-pulmonary" group and 632 5 ml in the atypical" pneumonia group. (Table IV)

Working capacity W_{170} sitting, averaged 812.5 kpm/min. in the non-pulmonary group and 625.6 kpm/min. in the atypical pneumonia group. The individual values have been plotted against heart volume, using the normal values earlier reported by Holmgren *et al.* (61a) (fig. 8) In all the subjects of the atypical pneumonia group W_{170} *lies to the left of the regression line*, but only one case (no. 7) fell outside two times standard error of estimate. In about half the cases of the non-pulmonary" group W_{170} *fell to the left of the above mentioned* regression line, one case (no. 12) lying just at the line representing twice standard error of estimate.

Orthostatic test Most of the cases in the non-pulmonary' group showed only moderate increase of the pulse rate in standing, the average value being 98.8 beats/min. Two cases (nos. 9 and 12) showed a very marked increase to 135 and 120 beats/min. respectively In the atypical pneumonia group, two cases (nos. 12 and 16) showed a very marked increase of the heart rate in standing to 135 and 130 beats/min. Four cases of this group (nos. 7 11 13 and 14) showed marked increase of the heart rate in standing (greater than 120 beats/min.)

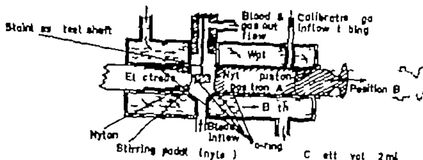


Fig 7 Cuvette for oxygen electrode, according to *Pitzele* showing method of sealing a stirring paddle and shaft into the analysis chamber For further explanation see text.

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In the present investigation conventional statistical methods have been used. The significance of differences between groups was tested by the t-test. Most methods of calculation were taken from Snedecor (126). The degree of probability was designated as follows:

$0.05 \geq p > 0.01$ probably significant.
** $0.01 \geq p > 0.001$ significant.
*** $0.001 \geq p$ highly significant.

Results

Circulatory studies

Electrocardiogram. ECG at rest was in the "non-pulmonary" group within the normal variation in 11 cases. In one (case no. 3) a slight ST and T deviation was observed, which was somewhat more marked in standing. One case (no. 12) showed moderate deviation of ST and T in standing, probably of the sympathicotonic type (61b). During and after the work test the ECG was normal in all patients.

In the "atypical" pneumonia group ECG was within normal variation in all cases at rest. In cases (nos. 12 and 14) marked ST and T deviation was observed in standing. During and after the work test ECG was normal in all cases.

Heart volume in prone position was on an average 737.5 ml in the "non-pulmonary" group and 632.5 ml in the "atypical" pneumonia group. (Table IV.)

Working capacity W_{170} sitting, averaged 812.5 kpm/min. in the "non-pulmonary" group and 625.6 kpm/min. in the "atypical" pneumonia group. The individual values have been plotted against heart volume, using the normal values earlier reported by Holmgren *et al.* (61a) (fig. 8). In all the subjects of the "atypical" pneumonia group W_{170} lies to the left of the regression line, but only one case (no. 7) fell outside two times standard error of estimate. In about half the cases of the "non-pulmonary" group W_{170} fell to the left of the above mentioned regression line, one case (no. 12) lying just at the line representating twice standard error of estimate.

Orthostatic test. Most of the cases in the "non-pulmonary" group showed only moderate increase of the pulse rate in standing, the average value being 98.8 beats/min. Two cases (nos. 9 and 12) showed very marked increase to 135 and 120 beats/min. respectively. In the "atypical" pneumonia group two cases (nos. 12 and 16) showed a very marked increase of the heart rate in standing to 135 and 130 beats/min. Four cases of this group (nos. 7, 11, 13 and 14) showed marked increase of the heart rate in standing (greater than 120 beats/min.).

Table IV Some anthropometric data in 16 subjects in the course following "atyp[illegible] [illegible]monia

Some anthropometric data in 12 subjects in the course following non pulmonary disease

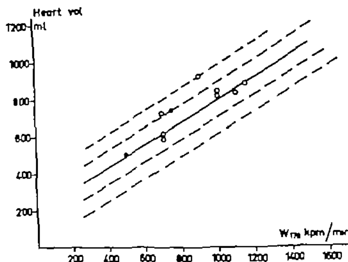


Fig. 8 Heart volume, ml (ordinate) in relation to rate of work at pulse rate of 170 beats/min (W_{170}) kpm/min (abscissa) Filled circles represent cases of the non-pulmonary group Straight line represents normal regression line, described by Holmgren *et al* 1957 (26) Broken lines indicate ± standard error of estimate and ± twice standard error of estimate.

The average pulse rate standing was in the non-pulmonary group 98.8 beats/min. In the atypical pneumonia group the pulse rate was on an average lower or 83.3 beats/min for the males but higher or 111.8 beats/min. for the females of the group. The average value for the whole group was 97.6 beats/min., which is not a statistically significant difference to the other group.

The influence of posture on W_{170} was studied in 5 cases of the non-pulmonary group and 7 cases of the atypical pneumonia group. (Table IV) The difference between the pulse rate sitting and in supine position on given load was almost the same in the two groups (8.2 and 9.1 beats/min. respectively) but was statistically probably significant (p = *) The rates of work at a pulse rate of 150 and 120/min. (W_{150} and W_{120}) were calculated in the way described by Holmgren and Svanborg (63). In the non-pulmonary group W_{120} supine was on an average 75 kpm/min. higher than W_{120} sitting, and W_{150} supine 80 kpm/min. higher than W_{150} sitting The corresponding values in the atypical" pneumonia group were plus 18 kpm/min. and plus 50 kpm/min. The number of cases studied in this way in each group are too small however to draw any statistical conclusions. But it may be said with some probability that the effects of posture during work were not more pronounced in the typical pneumonia group than in the non pulmonary group.

Pulmonary function

Static lung volumes The results from the determinations of lung volumes are given in table V The 12 subjects studied in the course following non-pulmonary disease show as a whole, only slight divergences

Table IV Some anthropometric data in 16 subjects in the course following 'atypical' pneumonia.

Case no.	Sex	Age years	Height, cm	Weight, kg	BSA m²	Hb-conc /100 ml	Heart volume ml	Pulse rate standing beats/min.	W_{70} sitting kpm/min.	Highest load in sitting position: kpm/min.	Duration min	Pulse rate beats/min.	Resp. rate breaths/min.	Orthostatic test pulse at work: load, kpm/min	sitting, beats/min.	supine beats/min
	M	37		67	1 [illegible]	16.19		60	[illegible]	[illegible]		79	29			
3	M	[illegible]	73	61 3	[illegible]	16.33			750	[illegible]		170	22			
	M	[illegible]	72		1 [illegible]	4.63			[illegible]	[illegible]		173	21			
	M	40		66.	1 79	16.63			96	[illegible]		140	[illegible]			
	M	1	78	67	76	1 44	750	96	66	[illegible]		140	20			
	M	[illegible]	64	67	72	13		90	[illegible]	[illegible]		134	20			
	F	21	66	37	1 [illegible]	13 63	[illegible]	134	56	250	9	71	1			
	M	40	[illegible]	63.	2	4.80		70	300	1300		84	76	900	122	129
	M			64	90	13	700	90	770	[illegible]		103	8			
	M	63	77	77	4	5 73		78	720	[illegible]			42	600	82	42
		60	150	40	48	80	500	11	300	400		84	22	250	1	130
13	F	21	63	61.	86	66	556	123	330	400		194	23	400	70	64
	F	40		61	82	80	61	81	450	400		183	44			
4	F	1	66	60	64	40	540	100	400	400			83	400	1	56
5		46	71	83	75	64	630	84	770	400		134	2	400	14	63
14	F	21	54		70	67	400	170	230	300		82	21	300	142	105
M		41.1	173	71	66			63	943	9.12		64	21 1	710	41	36
M		31	183		80	13 65	500		805	13		109 3	5	320	61	84
Group M		30	164	63		30	633	97	825	624		95	20	775	82	

Some anthropometric data in 12 subjects in the course following non pulmonary disease

Case no.	Sex	Age years	Height, cm	Weight, kg	BSA m²	Hb-conc /100 ml	Heart volume ml	Pulse rate standing beats/min.	W_{70} sitting kpm/min.	Highest load in sitting position: kpm/min.	Duration min	Pulse rate beats/min.	Resp. rate breaths/min.	Orthostatic test pulse at work: load, kpm/min	sitting, beats/min.	supine beats/min
1		21	163	56	60	1			750	400		96	30			
	M	36	71	63	76	66			80	250		96	23			
		64	73	67	63	63	615	90	700	400		77	21	600	49	62
	M	42	63	79	62	13.61	636	94	600	300		78	8	600	130	116
	M	11	63	66	95	6.63	648		900	300		64	22			
7	M	60	170	66.	79		730	64	700	600		62	24			
	M	44	72	67	79	43	61	84	800	600		106	27			
		26	79	76	96	63	643	96	600	300		62	25			
	M	21	177	75	92	80		125	870	600		163	24	600	62	53
		30	74	63	63	90		97	500	500		73		500	72	64
			67	90	90	77	67	90	670	600		77	24			
			177	79	96	80		30	600	800		71	21	900	73	64
M		36	79	73	67			84	41	81		78	30	640	66	47

BSA body surface area W_{70} working intensity at pulse rate of 70 beats/min

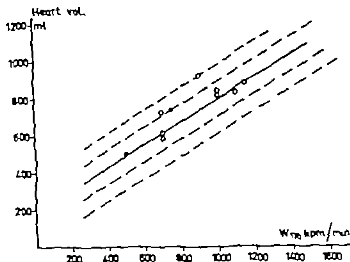


Fig. 8. Heart volume, ml (ordinate) in relation to rate of work at pulse rate of 170 beats/min. (W_{170}) kpm/min (abscissa). Filled circles represent cases of the non-pulmonary group. Straight line represents normal regression line, described by Holmgren *et al.* 1957 (26). Broken lines indicate ± standard error of estimate and ± twice standard error of estimate.

The average pulse rate standing was in the non-pulmonary group 98.8 beats/min. In the "atypical" pneumonia group the pulse rate was on an average lower or 83.3 beats/min. for the males but higher or 111.8 beats/min. for the females of the group. The average value for the whole group was 97.6 beats/min. which is not statistically significant difference to the other group.

The influence of posture on W_{170} was studied in 5 cases of the non-pulmonary group and 7 cases of the atypical pneumonia group. (Table IV). The difference between the pulse rate sitting and in supine position on given load was almost the same in the two groups (8.2 and 9.1 beats/min. respectively) but was statistically probably significant (p =). The rates of work at a pulse rate of 150 and 120/min. (W_{150} and W_{120}) were calculated in the way described by Holmgren and Strandell (63). In the non-pulmonary group W_{120} supine was on an average 75 kpm/min. higher than W_{120} sitting, and W_{150} supine 80 kpm/min. higher than W_{150} sitting. The corresponding values in the "atypical" pneumonia group were plus 18 kpm/min. and plus 50 kpm/min. The number of cases studied in this way in each group are too small however to draw any statistical conclusions. But it may be said with some probability that the effects of posture during work were not more pronounced in the "atypical" pneumonia group than in the non-pulmonary group.

Pulmonary function

Static lung volumes. The results from the determinations of lung volumes are given in table V. The 14 subjects studied in the course following "non-pulmonary" disease show as a whole only slight divergences

Table V Lungvolymes 1 BTPS mechanics of breathing nitrogen wash-out time and

Case	IRV	TV	ERV	VC Obs l.	VC % of pred.	FRC Obs. l	FRC % of pred.	RV Obs l	RV % of pred	TC Obs. l	TC % of pred	RV/TC [illegible] Obs. l	RV/TC % of pred
In 13 subjects in the course following non-pulmonary infections													
1	3 42	0 87	2.[illegible]	6 37	118	2.[illegible]	[illegible]	1 [illegible]	118	7 87	1	19	10[illegible]
	[illegible]	0 62	1 87	4.90	106	3.1	[illegible]	[illegible]	[illegible]	6 90	100	[illegible]	[illegible]
3	3.31	0 [illegible]	0 [illegible]	4 [illegible]	10[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	103	[illegible]	94
4	4 30	0 [illegible]	1 [illegible]	6.[illegible]	1[illegible]	2.67	103	1 [illegible]	1[illegible]	[illegible]	1[illegible]	[illegible]	[illegible]
6	3 63	0 87	2.[illegible]	6.70	103	2 49	98	1 27	[illegible]	7 67	94	19	[illegible]
	1 64	1 [illegible]	[illegible]	4.36	91	[illegible]	[illegible]	[illegible]	[illegible]	6.34	91	[illegible]	100
7	3 [illegible]	0 [illegible]	2.[illegible]	6 42	121	3 40	84	1 87	64	79	103	[illegible]	87
	3 93	41	1 49	5 13	104	2.[illegible]	[illegible]	1 44	79	6.67	87	[illegible]	42
9	2.73	0 64	[illegible]	4.[illegible]	[illegible]	2.18	103	1 10	40	6 [illegible]	[illegible]	1	[illegible]
10													
11	3. 1	41	1 30	4 61	[illegible]	3.1	104	0 [illegible]	[illegible]	3.64	119	13	[illegible]
1	5 66	0 61	[illegible]	6.[illegible]	104	2.41	106	3.[illegible]	137	7 61	118	[illegible]	1
M	3 [illegible]	0 [illegible]	1.[illegible]	5 [illegible]	10[illegible]	[illegible]	[illegible]	1 [illegible]	[illegible]	6 [illegible]	10[illegible]	[illegible]	[illegible]
Range	2.[illegible]-4 [illegible]	0 41 1 [illegible]	0 [illegible]-2.[illegible]	4.[illegible]-6 [illegible]	91 121	2.10-3 [illegible]	[illegible]-1[illegible]	[illegible] 2 [illegible]	[illegible]-137	[illegible]- [illegible]	[illegible]-1[illegible]	[illegible]-[illegible]	87 1[illegible]
In 16 subjects in the course following atypical pneumonia													
1	1 [illegible]	0 46	1 41	3 47		3.1	93	1 [illegible]	[illegible]	[illegible]	[illegible]		1[illegible]
	2.97	[illegible]	67	3.[illegible]	[illegible]	2.34	73	1 [illegible]	[illegible]	[illegible]	87	[illegible]	91
3	3 42	0 43	1 [illegible]	5.[illegible]	1[illegible]	2.[illegible]	[illegible]	2 [illegible]	112	7 34	11	[illegible]	[illegible]
	2.61	70	31	4.62	10[illegible]	3.[illegible]	[illegible]	67	[illegible]	[illegible]	97	37	[illegible]
5	1 [illegible]	0 44	0 [illegible]	[illegible]	73	3 [illegible]	77	1 [illegible]	61	[illegible]	77	[illegible]	1[illegible]
	1 [illegible]	46	0 62	[illegible]	77		87	34	1[illegible]	[illegible]	94	[illegible]	1[illegible]
7	1 34	0 37	87	2.[illegible]	101	2.[illegible]	81	1 13	[illegible]	4.87	81	[illegible]	1[illegible]
	[illegible]	0 42	43	87	[illegible]	2.[illegible]	87	2.87	1[illegible]	[illegible]	10[illegible]	[illegible]	1[illegible]
9	2.[illegible]	[illegible]	1 [illegible]	[illegible]	118	[illegible] 13	81	1 [illegible]	87	7 [illegible]	10[illegible]		[illegible]
	2.[illegible]	0 37	1 [illegible]	4 61	[illegible]	2.64	7	1 1	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
11	[illegible] 70		70	[illegible]	79	2.[illegible]	1[illegible]	1 64	13[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
12	1 [illegible]	0 [illegible]		[illegible]	[illegible]	2.[illegible]	91	[illegible]	87	4.[illegible]	[illegible]	[illegible]	1
13	0 [illegible]	0 44	0 [illegible]	1 [illegible]	48	1.43	[illegible]	81	[illegible]	3.37	[illegible]	3	1[illegible]
1	72	[illegible]	1 11	3 [illegible]	87	3 [illegible]		1 [illegible]	131	87	[illegible]	34	1[illegible]
15	1 [illegible]	0 41	1 [illegible]	3 10	[illegible]	[illegible]	1[illegible]	70	17	4.94	[illegible]	[illegible]	1[illegible]
16	1 87	[illegible]	1.7	31	[illegible]	1 70	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]
M	2.72	0 34	1 87	4.[illegible]	[illegible]	2.[illegible]	[illegible]	1 [illegible]	[illegible]	16	[illegible]	[illegible]	1[illegible]
Range	[illegible]-3 [illegible]	[illegible]-0 70	0 43-1 [illegible]	3 [illegible]-6 [illegible]	73-13	2.34-3.[illegible]	[illegible]-[illegible]	7 [illegible] 2.[illegible]	[illegible]-130	[illegible]- [illegible]	77 11[illegible]	[illegible]-[illegible]	73-13[illegible]
F	1 36	0 [illegible]	1	2.70	[illegible]	2.19	[illegible]	1 [illegible]	10[illegible]	4.[illegible]	[illegible]	[illegible].4	137
Range	[illegible]-1 87	43-0 7	0 [illegible]-1.73	1 [illegible]-[illegible]	48- 61	[illegible]-3 [illegible]	[illegible]-10[illegible]	[illegible]-1 70	[illegible]-131	2.87-4 97	[illegible]-[illegible]	[illegible]-[illegible]	[illegible]-1[illegible]
M	2.64	0 [illegible]	1 [illegible]	3.14	[illegible]	[illegible] 61	91	1 1	101	4.97		31	116

IRV inspiratory reserve volume, TV tidal volume ERV expiratory reserve volume VC vital capacity FRC functional residual
FVC forced vital capacity $FEV_{1.0}$ forced expiratory volume in one second FEV % FEV in per cent of FVC MMF maximal

from the material described by Grimby and Söderholm (53) Thus, vital capacity was on an average 5 32 l. BTPS or 109 % of predicted (p = *) and the quotient residual volume/total capacity was 23 % or 89 % of predicted (p = *)

The 16 cases in the "atypical pneumonia group showed slightly reduced values of *vital capacity functional residual capacity* and *total capacity* the mean difference from the predicted values of the whole group being statistically probably significant (p = *) Three cases (1 5 and 13) had values of vital capacity lower than twice S.D from the predicted normal value, 2 cases (5 and 13) had values of total capacity *lower* than twice S.D and one case (no 13) had a FRC lower than twice S.D from the predicted normal value. In comparison with the non pul monary group the atypical pneumonia group showed markedly reduced VC (difference *highly significant, p* = ***) and TC (difference significant, p = **)

The quotient *residual volume/total capa* city was in the "atypical pneumonia group 31 % or *116 % of predicted (p = *) In* four cases (6 8, 11 and 15) this quotient *was above what is considered the upper* normal range 35 % (14) The total capacity *was in these cases* within normal range In

nitrogen wash out index.

FRC		TLC		RV		FEV %		MBC		N_2 wash out time	$\frac{RV}{TLC}$
Litre	% of pred.	Litre	% of pred.	Litre	% of pred.	One L.	% of pred.	l./min.	% of pred.	min	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	single breath	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	single breath	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	—	[illegible]

[illegible] RV residual volume TC total lung capacity $\frac{RV}{TLC}$ [illegible] MBC maximal breathing capacity [illegible]

case no. 13 all lung volumes were significantly reduced but the residual quotient was at the upper normal limit. In comparison with the non-pulmonary group, the atypical" pneumonia group showed markedly increased quotient (difference highly significant p ≈ ***)

Maximum breathing capacity (MBC) was in the 12 cases in the non-pulmonary group on an average 185.8 l./min. (range 144—238 l./min.) or 118 % of predicted value (p ≈ **) The atypical" pneumonia group averaged 124.9 l./min. or 95 % of predicted value (not significant). No cases had values lower than twice S.D. When compared to the non-pulmonary group the mean value for the whole group of atypical pneumonia was significantly lower (p ≈ **)

Forced expiratory volume in one second (FEV 1.0) was, in the non-pulmonary" group, at an average 4.31 l./min. or 117 % of predicted (p ≈) The atypical" pneumonia group showed slightly reduced values, the mean for the whole group being 2.84 l or 88 % of predicted (p ≈ *) It may be noticed that the values for the females were lower and significantly reduced (at an average 2.38 l or 78 % of predicted, p ≈ **) in comparison to the males of the group,

who had values within normal range (3 30 1 or 98 % of predicted) Thus, 3 females (11 13 and 14) showed values lower than twice S.D from the predicted normal value In comparison to the non pulmonary group the average value of FEV 1 0 for the whole group was highly significantly reduced (p = ***)

Forced expiratory volume in one second in % of forced vital capacity (FEV %) was at an average 81 4 % (range 95—164 %) or 101 % of the predicted value in the non pulmonary group and 79 6 % or 96 % of predicted in the atypical pneumonia group (not significant) One male (case 9) and one female (case 14) had values lower than twice S.D from the predicted value. There was no significant difference between the two groups.

Maximal midexpiartory flow (MMF) averaged 4 93 l./sec. or 12 % of predicted for the non pulmonary group and 2 95 l / sec. or 85 % for the atypical pneumonia group The difference observed predicted value was statistically insignificant for the whole atypical pneumonia group but the females had significantly lower values (2.53 l./sec. or 64 % of predicted p = **) in comparison to the males of the group (3 41 l./sec. or 105 % of predicted value) Thus three females (cases 11 3 and 14) had values lower than twice S.D from the predicted normal value and one male (case 9) had a value just at the lower normal limit. In comparison to the non pulmonary group, MMF for the whole group was significantly lower (p = **)

Distribution of inspired gas (table V) Nitrogen wash-out time was for the non-pulmonary group on an average ~.70 min. (range 1 7—4 3) and for the atypical pneumonia group 3 3 min. (range 1 3—4.8) One case (no 4) in the non-pulmonary group and three cases (nos. 2, 13 and 15) in the atypical pneumonia group had a wash-out time above 4 minutes. No significant difference was observe between the two groups.

The wash-out index i.e the volume ventilated during nitrogen wash-out time per liter FRC was on an average 7 40 (range 4 31—9.22) in the non pulmonary group and 8 57 (range 6.2—10 95) in the atypical pneumonia group Two males (case 2 and 3) in the atypical pneumonia group had an index above the upper normal border (17) No significant difference was noticed between the groups. In some cases (no. 11 of the non pulmonary group and nos. 9 11 and 12 of the atypical pneumonia group) the single breath technique was used. The nitrogen concentration was the same in all these cases at the 750 and 1.250 cc points of expired volume (nitrogen difference < 2 %)

To Summarize the lung volumes of the atypical pneumonia group were more or less reduced in comparison with the non-pulmonary group The residual quotient was significantly higher in the atypical pneumonia group though the absolute residual volume in no case was above twice S.D of predicted value.

The dynamic spirometry was within normal limits in the non pulmonary group and slightly to moderately impaired in seven cases of the atypical pneumonia group The distribution of inspired gas was found to be slightly uneven in a few cases of the atypical pneumonia group but no significant difference between the groups was found.

Ventilation alveolar gas exchange diffusion blood gas tensions and anatomical blood shunt were studied at rest in supine position and during work in sitting position

in the non-pulmonary group (table VI) and in the atypical pneumonia group (table VII)

At an average work load of 550 kpm/min. (range 300—800) in the non-pulmonary group the heart rate increased to 146.0 (range 129—176) respiratory rate to 20.8 breaths/min. (range 14—32) and oxygen consumption ($\dot{V}_{O_2}$) to 1 511 ml/min. STPD (range 923—2.011) The corresponding values for the atypical pneumonia group were 481 kpm/min. (range 150—900) 146.8 (range 134—178) 25.8 (range 18—31) and 1 331 ml/min. (range 649—2.238)

The physiological dead space (V_D) was, in the non-pulmonary group at rest, on an average 150 ml. BTPS (range 100—226) or within normal limits and increased ordinarily during exercise in 9 cases (6, 110) In 3 cases (nos. 2, 6 and 7) the dead space was slightly reduced during work probably indicating non steady state The average value during work for the whole group was 201 ml. BTPS (range 78—383) which is within normal limits.

In the atypical" pneumonia group the dead space was normal at rest. The average value at rest was 145 ml BTPS (range 69—212) During exercise dead space increased ordinarily in 12 cases (nos. 8, 9 10 and 15) The average value during work for the whole group was 202 ml. BTPS (range 54—361) The increase of physiological dead space from rest to work is of the same magnitude in both groups, and there is no statistical difference between the groups. The relationship between dead pace and tidal olume (V /V) (42, 105 110) was somewhat high at rest in both groups the average for the non-pulmonary group was 0.39 (range 0.30—0.57) and for the atypical pneumonia group 0 41 (range 0.20—0.55) During exercise the quotient decreased to 0 14 (range 0.07—0.24) and 0 18 (range 0 02—0 36) respectively The quotient was above normal limits in 2 cases of the atypical" pneumonia group during exercise (cases nos. 11 and 13) but these could only perform a very moderate work (150 and 300 kpm/min. respectively) The average values for the two groups during exercise were within normal limits and the differences between the groups were not statistically significant.

Alveolar ventilation as indicated by P_{CO_2} and the $P_{I_{O_2}} - P_{A_{O_2}}$ difference was within normal limits at rest and during work in most cases of the two groups. One male (case no. 1) of the atypical pneumonia group with a normal P_{CO_2} at rest, showed manifest signs of hypoventilation during the exercise, as the P_{CO_2} increased to 53 mm Hg, which is above the upper normal limit (62) Ventilation ($\dot{V}_E$) was low in relation to oxygen consumption (28, 36, 138) and the arterial oxygen saturation was significantly reduced (84 %) (34) The $P_{I_{O_2}} - P_{A_{O_2}}$ pressure difference was increased both at rest and during exercise. This hypoventilation can not be explained by an increased dead space ventilation ($\dot{V}_D/V_T$ = 0.21 within normal limits) and no other plausible explanation can be offered. Two cases in the atypical" pneumonia group (cases nos. 7 and 10) showed signs of moderate hyperventilation during exercise, as indicated by decreased P_{CO_2} (29 and 28 mm Hg respectively) and increased ventilation (52.8 and 54.5 l BTPS/min. respectively) in relation to oxygen consumption. One case of the non-pulmonary" group (case no. 7) had at rest P_{CO_2} of 47 mm

Table 71 Ventilation, diffusing capacity and related values in 12 subjects in the course following "non pulmonary" infections

Case no.	Work load, kpm/min	Pulse rate, min	Respiratory rate, breaths/min	V_E l BTPS/min	V_T ml BTPS	V_D ml BTPS	V_D/V_T	V_{O_2} ml/min STPD	RQ	V_E l BTPS / V_{O_2} l STPD	P_{aO_2} mm Hg	S_{aO_2} %	pH, units	P_{aCO_2} mm Hg	D_{LCO} ml STPD/min/mm Hg Obs.	% of pred.	D_{LCO}/m² BSA Obs.	% of pred.	D_{LCO}/l STPD alv. vol. Obs.	% of pred.	Q_s/Q_T %	Gas pressure differences mm Hg				Standard bicarbonate, mE/l
1	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
3	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
5	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
6	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
7	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
9	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
10	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
11	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
12	Rest / [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
M	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Range	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Symbols and abbreviations according to Pappenheimer et al. [illegible] 1950 [illegible]

Table 5.11 Ventilation, diffusing capacity and related data in 16 subjects in the year following "atypical" pneumonia.

or a the upper normal limit and the was slightly reduced (94 mm Hg) the arterial oxygen tension was normal mm Hg) During exercise this case had ever a normal alveolar ventilation as cated by the alveolar gas tensions.

he arterial oxygen tension (P_{O_2}) in non pulmonary group was at rest on verage 94 mm Hg (range 92—100) and ng work 96 mm Hg (range 9?—106) ch is within normal limits and well in eement with earlier reported normal ma ls (15 62, 79 82, 106, 107)

n the atypical pneumonia group the age value at rest was 77 mm Hg (range -97) or lower than reported earlier (62) ee cases (nos. 6, 11 and 13) had signifi ly low values During exercise the P_{O_2} eased to 84 mm Hg (range 60—10?) cases except three (cases nos 3 6 and had values within normal limits.

he mean value at rest, for the atypical umonia group differed highly signifi ly (p = ***) from the non pulmon group, the differences being 17 mm The difference between the groups dur exercise was 12 mm Hg or statistically ificant (p = **)

he arterial carbon dioxide tension CO_2) was at rest in both groups almost in normal limits (62 82) (mean value and 35 mm Hg respectively) During k the average value for the non pul ary group was 38 (range 30—46) and the atypical pneumonia group 36 ge 28—53) In this group case no 1 a value above and cases nos. 7 and 10 es below the normal range of variation. se deviations were probably caused by effect of hypo- and hyperventilation. No istically significant difference was found ween the groups at rest and during work.

The arter. pH was in the non pul monary" group at rest on an average 7 4? (range 7 399—7 4?6) and during exercis 7 355 (range 7 259—7.3?7) In one case a rest (case no. 2) and one case at work (ca no. 4) the pH lay below the lower norm limit (62)

In the "atypical" pneumonia group pH rest varied between 7 394—7 473) (me value 7 427) and during exercise betwe 7.227—7 397 (mean value 7.335) In th cases (nos. 1 10 and 14) the pH was belo the range of normal materials. The S.B. w in cases 10 and 14, markedly reduced. N statistically significant difference of pH rest and during exercise were found betwe the two groups.

Standard bicarbonate (S.B.) varied at r in the non-pulmonary group from 21.6 6.0 (mean value .3 8) and in the atypic pneumonia group between 21 0— (mean value .2 6) and decreased dur exercise in both groups to an average of 1 (range 16.8—21 3) and 18.9 (range 14.1 21 3) S.B was in cases nos 10 and markedly reduced during work. No stati cally significant difference between groups was noticed at rest and during ex case.

Anatomical shunt The flow through shunt was in the non pulmonary group an average 3 6 % (range 2 3—6.4) or agreement with earlier reported non series (13 15)

In the atypical pneumonia group flow through the shunt was on an aver 9 9 % (range 6.5—15 3) or significan higher than that found in the non-p monary group. In one case (no 13) shunt was calculated to be 15 3 % but c rection of $P_{A_{CO_2}}$ according to Riley *et* (104) and others (82 111) was howev

considered to be of little importance in this case and thus omitted.

To summarize ventilation was within normal limits in the two groups, except in one case of the atypical pneumonia group who showed signs of alveolar hypoventilation with slight CO_2 retention and in two cases of the same group who had arterial gas tensions indicating a slight hyperventilation. P_{O_2} was in the atypical pneumonia group on an average significantly lower in comparison to that found in the non-pulmonary group both at rest and during exercise, but no significant difference was found between the groups as regards the P_{CO_2}. Anatomical shunts within normal range were found in the non-pulmonary group, but varied between 6—15 % in the atypical" pneumonia group.

Diffusion capacity of the lungs for carbon monoxide (D_{LCO})

The D_{LCO} in the non-pulmonary group was at rest on an average 20.47 ml. STPD/min./mm Hg (range 13.37—25.41) or 112 % of the predicted normal value. D_{LCO} /m² BSA was on an average 10.79 ml. STPD/min./mm Hg/m² BSA or 116 % of predicted normal value and D_{LCO} /l BTPS midcapacity averaged 5.29 ml. STPD/min./mm Hg/l midcapacity or 94 % of predicted value.

During work D_{LCO} increased in all cases and averaged 37.01 ml. STPD/min./mm Hg (range 27.27—53.70) or 106 % of predicted normal value. D_{LCO} /m² BSA increased to 19.66 ml. STPD/min./mm Hg/m² BSA or 113 % of predicted value and D_{LCO} /l BTPS midcapacity to 10.45 ml STPD/min./mm Hg/l midcapacity or 99 % of predicted normal value.

The difference observed-predicted value of D_{LCO} /m² BSA was probably significant (p =) at rest. The corresponding difference D_{LCO} /midcapacity was not significant. During work, the difference observed-predicted value was probably significant (p = *) only for D_{LCO} /m² BSA.

Thus, the values of the diffusion capacity in this group at rest and during exercise are very close to those reported by Donevan *et al* (38) and they also agree fairly well with those reported by others who have used the steady state CO technique (16, 43, 90).

The D_{LCO} at rest in the "atypical" pneumonia group was on an average 11.52 ml STPD/min./mm Hg or 65 % of predicted normal value. D_{LCO} /m² BSA averaged 6.53 ml. STPD/min./mm Hg/m² BSA or 68 % of predicted and D_{LCO}/midcapacity averaged 4.06 ml. STPD/min./mm Hg/l midcapacity or 69 % of predicted normal value.

During exercise D_{LCO} increased to an average of 22.71 ml. STPD/min./mm Hg or 78 % of predicted normal value. D_{LCO} /m² BSA increased to 12.92 ml. STPD/min./mm Hg or 86 % of predicted and D_{LCO} /l BTPS midcapacity to 8.09 ml STPD/min./mm Hg/l midcapacity or 85 % of predicted normal value.

Statistically the difference observed-predicted value for D_{LCO} was highly significant (p = ***) at rest as well as during exercise. The corresponding difference D_{LCO} /m² BSA was *highly significant at rest* (**) and significant during work (p =). *The difference observed-predicted value for* D_{LCO}/midcapacity was highly significant (p = ***) *at rest* and significant during work (p = **).

The differences in D_{LCO}, D_{LCO} /m² BSA and D_{LCO} /l midcapacity at rest between the "atypical" pneumonia group and the "non-pulmonary" group were statistically significant (p = ***). During work the cor

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In the atypical pneumonia group the average value at rest was 77 mm Hg (range 62—97) or lower than reported earlier (62) Three cases (nos 6, 11 and 13) had significantly low values. During exercise the P_{O_2} increased to 84 mm Hg (range 60—102) All cases except three (cases nos 3 6 and 13) had values within normal limits.

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The arterial pH was in the non-pulmonary group at rest on an average 432 (range 7 399—7 476) and during exercise 7.355 (range 7 239—7 387) In one case at rest (case no. 2) and one case at work (case no. 4) the pH lay below the lower normal limit (62)

In the atypical pneumonia group pH at rest varied between 7 394—7 473) (mean value 7 427) and during exercise between 7 227—7 397 (mean value 7 335) In three cases (nos. 1 10 and 14) the pH was below the range of normal materials. The S.B was, in cases 10 and 14, markedly reduced. No statistically significant difference of pH at rest and during exercise were found between the two groups

Standard bicarbonate (S.B) varied at rest in the non pulmonary group from 22 6—26.0 (mean value 23 8) and in the atypical" pneumonia group between 21 0—24.5 (mean value 22 6) and decreased during exercise in both groups to an average of 19.4 (range 16.8—21 3) and 18 9 (range 14.8—21 3) S.B was in cases nos. 10 and 14 markedly reduced during work. No statistically significant difference between the groups was noticed at rest and during exercise.

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The mean value at rest, for the atypical pneumonia group differed highly significantly (p = ***) from the non pulmonary group the differences being 17 mm Hg. The difference between the groups during exercise was 12 mm Hg or statistically significant (p = **)

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responding differences between the groups were statistically highly significant (p = ***) higly significant (p =) and significant (p = **) Fig. 9)

To summarize the results of the study on the diffusion capacity in the non-pulmonary group agreed well with those previously reported at rest as well as during exercise. The atypical pneumonia group had, in comparison to the non-pulmonary group, significantly low D_{LCO} both absolutely an in relation to body surface area and midcapacity at rest and during exercise.

Discussion

The purpose of studying a control" group consisting of convalescents after infectious diseases without signs of pulmonary involvement, was to find out, if convalescence *per se* could have any significant influence on circulatory and pulmonary function. Some investigations in this field have been presented. Thus, Köhler (75) showed, that electrocardiographic changes were common after acute infectious diseases.

Bengtsson (19) studied the effect of convalescence after various infectious diseases on the physical working capacity (W_{170}) and found it, in adults, to be significant low in comparison to normals. He also studied orthostatic reactions, and found an increase of heart rate from supine to upright position that averaged about 20 beats/min. In about one-half of the subjects with increased heart rates, concomitant electrocardiographic changes were found.

The present investigation has shown, that some cases of the non-pulmonary" group had a slight, but not significantly reduced physical working capacity in sitting, both absolutely and in relation to heart volume. Varying, but as whole moderate orthostatic reactions at rest (standing) as well as during work were found, which is in agreement with the results presented by Bengtsson. In contrast, Beregård and Svanborg (26) in recent preliminary studies on hospitalized patients, could show no corresponding orthostatism.

Some cases in the atypical" pneumonia group (nos. 7 and 16) showed a significantly low working capacity in relation to heart volume and marked orthostatic reactions at rest as well as during work, but as a whole, the changes in working capacity and the orthostatic reactions were of about the same magnitude in the two groups.

Marked electrocardiographic changes at rest in standing of sympaticotonic type were observed only in a few cases of each group, and no significant difference between the groups was found in this respect.

The pulmonary function in the non-pulmonary group was found to be within the range of earlier presented normal series (13, 42, 79 82, 105) Consequently the data of this group may be used as normal values, being related to in the analysis of the results obtained in the atypical" pneumonia group.

The most important disturbances found in the atypical pneumonia group in comparison to the non-pulmonary" group are the ***moderate anatomical shunts*** and the significantly ***decreased diffusion capacity*** at rest and during exercise, as well in absolute terms as in relation to body square area and midcapacity

The presence of anatomical shunt may be explained by way of the patho-anatomical changes generally seen in the interstitial tissue and the alveoli during the course of virus pneumonia (66, 67 98, 127) Numerous small areas with non-ventilated alveoli atelectasis) due to filling up with exudate and/or collapse may probably remain in the

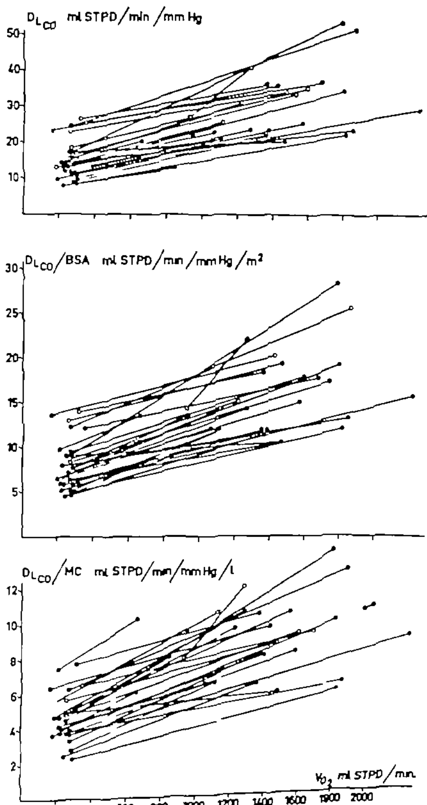


Fig 9 Pulmonary diffusion capacity for carbon monoxide, D_{LCO} ml STPD/min/mm Hg, D_{LCO}/BSA and D_{LCO}/ midcapacity in relation to oxygen uptake (V_{O_2}) ml STPD/min. at rest in supine and during exercise in sitting position. Filled circles represent the cases of the atypical pneumonia group, open circles the cases of the non-pulmonary group

capacity which might indicate, that a thickening of the pulmonary membranes and/or a change in their permeability may be present in this material. These changes may be a contributing cause of the observed decrease of D_{LCO} but it is difficult to say whether qualitative or quantitative causes are predominant. Consequently it would be of interest to study the membrane component of diffusion (D_M) in subjects having suffered from atypical pneumonia. Fortunately this can be calculated from measurements of D_{LCO} at different alveolar oxygen tensions (44, 45 115)

The alveolar mean capillary oxygen pressure difference may be calculated from the D_{LCO} and the oxygen consumption, V_{O_2} according to the equation

$$P_{A_{O_2}} - P_{c_{O_2}} = \frac{V_{O_2}}{1.23 \times D_{LCO}} \qquad (2)$$

These differences are given in table VI and VII and averaged for the non-pulmonary group at rest 11 mm Hg and 34 mm Hg during exercise, which is in close agreement with those of an earlier normal series (82). The corresponding values for the "atypical" pneumonia group were 18 mm Hg and 47 mm Hg. These values are considerably higher than those found in the non-pulmonary group, but indicate that there is still a diffusion reserve at the rates of work investigated (82). In some cases (nos 3, 4 and 8) however these oxygen differences are significantly increased, indicating, that diffusion may be impaired to such degree, that it might be a possible limiting factor of oxygen transport. (Fig. 10.) Here the individual values of D_{LCO} in the two groups are plotted against the corresponding $\dot{V}_{O_2}$. The straight lines (iso-gradient lines) are derived according to Linderholm (82) by inserting in equation 2 different values of $P_{A_{O_2}} - \bar{P}_{c_{O_2}}$ up to 70 mm Hg and calculating D_{LCO} for different values of $\dot{V}_{O_2}$. An oxygen pressure difference of 70 mm Hg is considered to be the the highest difference compatible with an adequate oxygen transport (82, 106). From the figure it can be seen, that the values of the two groups differ considerably most cases of the atypical pneumonia group being closer to this maximal iso-gradient line.

The degree of impairment of alveolar ventilation may be expressed by the value of the mouth-alveolar oxygen difference, $P_{I_{O_2}} - P_{A_{O_2}}$ (82). The average value of this difference was found to be within normal limits both at rest and during exercise in the "atypical" pneumonia group, except in one case (no. 1) thus indicating a fairly normal alveolar ventilation. No significant difference was found between the groups. In case no. 1 the difference was somewhat increased at rest as well as during work, indicating slight impairment of ventilation. The nitrogen wash-out time and intrapulmonary mixing index were, however within normal limits. The same patient also showed signs of hypoventilation during exercise, as the arterial CO_2 tension was above upper normal limit and oxygen saturation was low. No plausible explanation of this hypoventilation was found, but it may be pointed out, that it seems to have been temporary as the standard bicarbonate was not increased to such a degree as to compensate the respiratory acidosis completely

The alveolar-arterial oxygen pressure difference, $P_{A_{O_2}} - P_{a_{O_2}}$ found in the "non-pulmonary" group was of the same magnitude as is earlier reported in normals as well at rest as during exercise (14, 31 79 82, 105). In the "atypical" pneumonia group

affected parts of the lungparenchyma after the acute phase of infection, even if the parenchymal lesions visible on x ray during this phase have disappeared more or less The perfusion through these non ventilated small areas may probably be reduced more or less (4 112) but the remaining perfusion may be equivalent to the shunt. The size of this shunt was estimated as the venous ad mixture breathing 100 per cent oxygen (20)

The total lung capacity was significantly low in the atypical pneumonia group when compared to the non pulmonary group This may essentially be a result of a decrease in vital capacity as the residual volume was found to be within normal range. The explanation of these changes will possibly be found in a combination of the effect of the above mentioned small areas of atelectasis and inactivity The ratio RV/TC was significantly increased, which may either be due to reduction of the vital capacity or to an increase of the absolute value of the recidual volume. However only a few cases of the group (Nos 6, 8 11 and 14) were found to have a somewhat increased residual volume, why the increased ratio above all may be explained by a reduction of the vital capacity

The mechanics of breathing was found to vary considerably within the atypical pneumonia group. Most females of the group showed significantly reduced FEV 1 0 and MMF which influenced the corresponding average value of the whole group to differ significantly from that of the "non pulmonary group MBC was slightly reduced in some cases (nos 6, 11 13 and 14) three of which were females (the same cases having markedly reduced MMF) FEV % which depends more on maximal ventilatory flow than on lung volume, was on the other hand normal or almost normal in most cases, and no significant difference was found between the groups thus indicating, that obstructive changes probably may have been of little importance in this material. The observed reduction of FEV 1 0 MBC and MMF especially among the females, may to some extent, be explained by poor co-operation due to weakness during convalescense. The presence of more or less pronounced changes of restrictive type can, however not be excluded the observed slightly reduced lung volume in some cases speaking in favour of such changes.

The diffusion capacity for CO was found to be significantly reduced in the atypical pneumonia group both at rest and during submaximal work as well in absolute terms as in relation to BSA and midcapacity The diffusion capacity of the lungs is influenced by factors determining diffusion of gases between the alveoli and the pulmonary capillary blood. Thus, a *reduction of the surface area* for diffusion due to loss of alveoli and/or a decrease in the number of capillaries in contact with functioning alveoli will lead to a quantitative decrease in the diffusion capacity Any lesions in the alveolo-capillary membranes, leading to a *thickening of these membranes* and thus to an increase of the distance for diffusion will cause a qualitative decrease of $D_{L_{CO}}$ Such lesions may also cause a *change in the permeability* of the tissues making up the alveolo-capillary membranes resulting in a decrease of the diffusion capacity

The observed decrease of diffusion capacity in the atypical pneumonia group must, to some extent, depend upon a reduction of the diffusion area due to loss of functioning alveoli in the affected parts of the lung parenchyma. However also in relation to the observed midcapacity there was a significant reduction of the diffusion

Hg during air breathing at rest. The component due to anatomical shunts (ranging between 6 and 15 % of cardiac output) would then lie between about 10 and 20 mm Hg and constitute about half of the total observed A—a difference. This is in close agreement with earlier reported studies on the A—a difference and its components in patients with chronic pulmonary tuberculosis, emphysema and carcinoma of the lung (135). Thus, Wilson *et al.* found such cases to be associated with a larger pure shunt than normal, ranging between 2 and 11 per cent of cardiac output. The component of the A—a difference due to shunts of this magnitude lies, according to Briscoe (31) between 4 and 15 mm Hg while breathing air.

The other part of the A—a difference in this material should include a membrane component due to the observed impairment of diffusion, which in some cases may amount to only few mm Hg during air breathing. But in other cases with more severe impairment of diffusion and with more or less pronounced disturbances in ventilation and/or in distribution of gas within the lung, it may be possible that, since the alveolar oxygen tension can reach low values in very poorly ventilated alveoli, there is an appreciable membrane component in the total A—a difference (79). This is illustrated by the fact, that when breathing low oxygen (lower than that of air) the membrane component will increase and constitute greater part of the A—a difference (13, 79, 106).

The rest of the A—a difference (about 10—15 mm Hg) would then be due to uneven $\dot{V}_A/\dot{Q}$ ratios within the lungs. It is earlier pointed out, that uneven ventilation/perfusion ratios may exist in healthy individuals, giving the resulting component of the A—a difference a magnitude of about 9 mm Hg (31). Consequently in the "atypical" pneumonia cases this component was found to be some mm Hg greater indicating that more pronounced ventilation/perfusion disturbances existed in these subjects, even though the results of the N_2-wash-out studies were mostly within normal limits.

In a study on the cardio-pulmonary function in sarcoidosis Holmgren and Svanborg (63) found a tendency to orthostatic reactions both at rest in standing and during work in sitting position as compared with supine position. As the $D_{L_{CO}}$ during exercise was determined in sitting they suggested that the observed reduction of this capacity partly might have been an effect of a decrease in capillary blood volume due to large orthostatic blood volume shifts. It was not possible, from the data available at that time, to decide whether this orthostatism was caused by the sarcoidosis or by inactivity. No similar decrease of the diffusion capacity was found during exercise in sitting in the non-pulmonary group of the present material though several cases of this group showed signs of slight to moderate orthostatic reactions of the same type as described by Holmgren and Svanborg. In the "atypical pneumonia group some cases showed more pronounced orthostatic reactions which probably may have contributed in some degree to the observed reduction of the diffusion capacity in these subjects. It is, however at present difficult to discuss the importance of such a reduction of $D_{L_{CO}}$ caused by orthostatism as yet no reliable investigations of this probleme have been published.

Holmgren and Svanborg further made a thorough analysis of the circulatory and

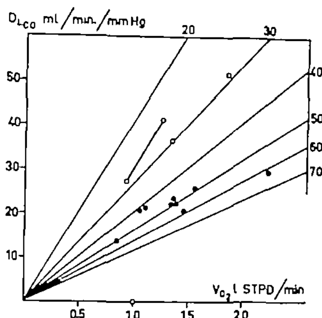


Fig 10 Pulmonary diffusion capacity for carbon monoxide, $D_{L_{CO}}$ ml STPD/min/mm Hg during exercise in relation to the corresponding oxygen uptake (V_{O_2}) ml STPD/min. The straight lines (iso-gradient lines) correspond to different values of the $P_{A_{O_2}} - P_{C_{O_2}}$ difference, and are derived according to the text. Filled circles represent the cases of the atypical pneumonia group, opened the cases of the non-pulmonary group.

thus A—a difference was found to be considerably increased at rest as well as during exercise and averaged 33 and 31 mm Hg respectively It may be observed that the difference is a little smaller during exercise than at rest, propably depending upon the fact, that P_{O_2} increased slightly more from rest to exercise than $P_{A_{O_2}}$ A similar slight increase of P_{O_2} during submaximal exercise has earlier been reported (7 82) but was not observed by Holmgren and Linderholm (62) This divergence may be explained by the fact, that the P_{O_2} measurements of the last mentioned series were done during heavier work.

The A—a difference can be regarded as composed of two components (79) 1) A venous admixture component and 2) a membrane component. The first one is not entirely due to pure or anatomical shunt, but includes the effect of uneven ventilation in relation to perfusion ($\dot{V}_A/\dot{Q}_c$ ratios) The second component includes the rate of diffusion of gases across the alveolo-capillary membranes and the rate of reaction of oxygen with haemoglobin. In normals at rest during air breathing the membrane component is small and does not amount to more than about one mm Hg (79) The true (anatomical) shunt has been estimated by Berggren (20) and Wilson *et al* (135) to be about 1—2 % of cardiac output, producing an A—a difference of only one or two mm Hg while breathing air The rest of the A—a difference should then be due to uneven V_A/Q – ratios constituting the largest part of it. Thus, Briscoe (31) found this component of the A—a difference in 18 studies of 6 normal subjects to average 9 mm Hg, assuming an even perfusion of the lung

In the present material of atypical pneumonias the A—a difference averaged 33 mm

Hg during air breathing at rest. The component due to anatomical shunts (ranging between 6 and 15 % of cardiac output) would then lie between about 10 and 20 mm Hg and constitute about half of the total observed A—a difference. This is in close agreement with earlier reported studies on the A—a difference and its components in patients with chronic pulmonary tuberculosis, emphysema and carcinoma of the lung (135). Thus, Wilson *et al* found such cases to be associated with a larger pure shunt than normal, ranging between 2 and 11 per cent of cardiac output. The component of the A—a difference due to shunts of this magnitude lies, according to Briscoe (31) between 4 and 15 mm Hg while breathing air.

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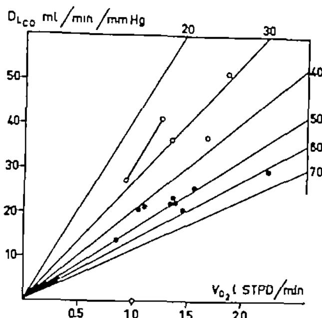


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In the present material of atypical pneumonias the A—a difference averaged 33 mm

15 % of cardiac output were found. The lung function was not impaired to such a degree as to be a limiting factor of the oxygen transport.

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respiratory functions and their integration in the solution of the oxygen transport during exercise, which was expressed by a series of equations. With the aid of these they could analyse which part limits the oxygen transport if such a limitation was found. In analogy with this, and from the results obtained in the present material it is obvious that the ability to transport oxygen in subjects who have suffered from atypical pneumonia, usually is not limited by respiratory functions. In a few cases, however the diffusion capacity was impaired to such a degree, and the shunt was of such a magnitude, as to have been possible limiting factors for the oxygen transport, either separately or in combination. Otherwise this may have been limited by circulatory factors.

Finally a question of importance to be answered, is if the disturbances of the lung function observed immediately after the acute stage of pneumonia will persist later in the course following the acute phase, or in other words, if the interstitial lesions of affected parts of the lungs will be more or less permanent, possibly due to organisation. The first three cases of the group seem to speak in favour of this. They were taken to the laboratory more than one year after the end of acute phase (owing to certain practical circumstances) No new affections of the lungs had occured during this time interval, but they were shown to have disturbances of the lung function of the same type as in those studied only some weeks after the acute phase. It must be pointed out, however that it is difficult to say with certainty that the changes of lung function found in these three cases actually resulted from their actual pneumonia. To be able to answer the above question more accurately a follow-up study on the lung function in some cases of the atypical pneumonia group has been made. The results from this investigation will be presented and discussed in the third chapter

Summary

1 12 subjects, constituting a non-pulmonary group and 16 subjects, 9 males and 7 females, constituting an atypical pneumonia group were investigated at various time in the course following the acute phase of the actual infection with series of cardio-pulmonary function tests. The non pulmonary group consisted of convalescents after infectious diseases with no involvement of the lungs. In the atypical pneumonia group most cases had suffered from primary atypical pneumonia with lesions in the lungs probably of interstitial pneumonitis type. The x ray picture was normalized or almost normalized at the time for investigation.

2 The rate of work at a pulse rate of 170/min (W_{170}) was in the non pulmonary group normal or almost normal. W_{170} in the atypical pneumonia group was in relation to heart volume somewhat low Slight to moderate orthostatic reactions as well at rest in standing as during work in sitting were a little more frequent in the atypical pneumonia group.

3 The pulmonary function was in the non pulmonary group as a whole in close agreement with earlier normal materials

4 The static lung volumes in the atypical pneumonia group were slightly reduced and certain distrurbances in the mechanics of breathing could not be excluded.

Alveolar ventilation was normal in most cases. The diffusion capacity of the lungs was reduced at rest and during exercise as well in absolute terms as in relation to BSA and midcapacity

Anatomical shunts ranging from 6 to

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studied in the laboratory immediately after normalization of fever (18 a). The x-ray picture was at that time not quite normalized. At the second investigation (18 b) about two weeks later the x-ray picture was practically normalized. On a third test occasion two months later the x-ray picture was normalized, but the subject was still incapacitated for work due to cough and fatigue.

Methods

Spirometry, analysis of forced expiratory spirogram, measurements of the anatomical shunt and the diffusion capacity for carbon monoxide were performed according to the methods described in the first chapter (1–4, 11–16, 24, 27). Normal values were predicted in the same way as described in this chapter (10, 21–24).

When *the anatomical right-left shunt* $\left(\frac{\dot{Q}_A}{\dot{Q}_T}\right)$ in the lungs was more than 15 per cent of the cardiac output, the alveolar partial pressure for CO_2, calculated on the assumption that $P_{a_{CO_2}} \approx P_{A_{CO_2}}$ was corrected in the following way (28). By use of the known value of the shunt, the CO_2 content of the mean capillary blood ($C_{c_{CO_2}}$ vol. %) was calculated from the formula

$$\frac{\dot{Q}_A}{\dot{Q}_T} = \frac{C_{c_{CO_2}} - C_{a_{CO_2}}}{C_{c_{CO_2}} - C_{\bar{v}_{CO_2}}}$$

assuming an arterio-venous CO_2-difference of 4 ml/100 ml. $\dot{Q}_A$ = blood flow through right-left shunt, $\dot{Q}_T$ = total capillary blood flow. $C_{c_{CO_2}}$, $C_{a_{CO_2}}$ and $C_{\bar{v}_{CO_2}}$ indicate CO_2-content in pulmonary capillary, arterial and mixed venous blood respectively. From the value of $C_{c_{CO_2}}$ the corresponding P_{CO_2} was estimated from the nomogram given by Dill *et al.* (9). This value for P_{CO_2} was considered to be a more correct estimate of $P_{A_{CO_2}}$. The only case (no. 18 a and b) of the present series, in which correction was thought to be necessary had a shunt of about 20 per cent of cardiac output. The magnitude of the correction, corresponding to this shunt, was 1 mm Hg or of about the same size as the error of the method used for determining $P_{a_{CO_2}}$ (± 1 mm Hg).

The analytical methods were the same as those reported in the first chapter, except the determination of the arterial oxygen tension ($P_{a_{O_2}}$). In the present investigation this determination was made with a Clark electrode (8) using a mylar membrane (31). The measurement was made in a Severinghaus stainless steel cuvette (33) kept at constant temperature in Yellow Springs Company water bath[1] with an I. L. Meter[2]. Immediately after withdrawal of the blood. The error of a single determination of P_{O_2} at high range of oxygen tensions (500—700 mm Hg) was estimated from duplicate readings on equilibrated blood to be ± 1.0 %. In the low range (O_2 tensions 60—100 mm Hg) the error was estimated to be ± 0.5 %.

The determination of *the pulmonary capillary blood volume* (V_C) and *the membrane diffusion capacity* (D_M) was made according to the method of Roughton, Forster *et al.* (14, 15, 34) as modified by Bates *et al.* (2). By measuring the pulmonary diffusion capacity for monoxide ($D_{L_{CO}}$) at two different alveolar oxygen tensions these

[1] Commercial production model built by Yellow Springs Instrument Company, Yellow Springs,

CHAPTER II

The diffusion capacity of the pulmonary membrane and the pulmonary capillary blood volume in the course following atypical pneumonia

Introduction

In the first chapter it was shown that in subjects, who had suffered from atypical pneumonia probably of interstitial or viral type the pulmonary diffusion capacity for CO may be reduced, both in absolute terms and in relation to lung volume. The possible causes for this reduction of $D_{L_{CO}}$ were discussed and it was concluded that the active diffusion area (= the number of functioning capillaries in contact with functioning alveoli) must be reduced. These subjects also had anatomical shunts in the lungs from 6 to 15 per cent of the cardiac output, indicating that areas of non ventilated alveoli remained in the affected parts of the lung tissue after the end of the acute phase of infection. However the fact that $D_{L_{CO}}$ even in relation to the midcapacity of the lungs, was reduced, was suggested to indicate that changes of the thickness and/or permeability of the alveolo-capillary membrane might have been contributing factors In order to get more information about the underlying changes, pulmonary membrane diffusing capacity (D_M) and pulmonary capillary blood volume (V_C) were studied in eight cases after atypical pneumonia.

Normal values for D_M and V_C have been reported earlier (2 5 12, 20 25 26 29) but no information about the size of these components after pneumonias seem to have been presented.

Material

Total pulmonary diffusion capacity diffusion capacity of the pulmonary membrane, capillary blood volume and the anatomical shunt was studied in eight subjects, six females and two males, at various times in the course following the acute phase of atypical pneumonia. The mean age of the group was 34 (range 19—50) Before the actual pneumonia, all subjects had been quite healthy as respects the cardio-pulmonary system. The cold hemagglutination was positive, according to the criteria discussed in the first chapter in all cases but one (case no 21) who had a psittacosis pneumonia one year before the cardio-pulmonary investigation. The clinical diagnosis in this case was verified both from serological and epidemiological point of view The x-ray picture was normalized 3 months after the end of acute phase. Cases 13 14 and 15 belong to the atypical pneumonia group presented in the first chapter and were taken to this second investigation about half a year after the first one. Case no. 18 was first

studied in the laboratory immediately after normalization of fever (18 a). The x ray picture was at that time not quite normalized. At the second investigation (18 b) about two weeks later, the x ray picture was practically normalized. On a third test occasion two months later the x ray picture was normalized, but the subject was still incapacitated for work due to cough and fatigue.

Methods

Spirometry analysis of forced expiratory spirogram, measurements of the anatomical shunt and the diffusion capacity for carbon monoxide were performed according to the methods described in the first chapter (1, 4, 11, 16, 24, 27). Normal values were predicted in the same way as described in this chapter (10, 21 24).

When *the anatomical right-left shunt* $\left(\frac{\dot{Q}_A}{\dot{Q}_T}\right)$ in the lungs was more than 15 per cent of the cardiac output, the alveolar partial pressure for CO_2, calculated on the assumption that $P_{aCO_2} \approx P_{ACO_2}$ was corrected in the following way (28). By use of the known value of the shunt, the CO_2 content of the mean capillary blood ($C_{\bar{c}CO_2}$ vol. %) was calculated from the formula

$$\frac{\dot{Q}_A}{\dot{Q}_T} = \frac{C_{\bar{c}CO_2} - C_{aCO_2}}{C_{\bar{c}CO_2} - C_{\bar{v}CO_2}}$$

assuming an arterio-venous CO_2-difference of 4 ml/100 ml. $\dot{Q}_A$ = blood flow through right left shunt, $\dot{Q}_T$ = total capillary blood flow $C_{\bar{c}CO_2}$, C_{aCO_2} and $C_{\bar{v}CO_2}$ indicate CO_2-content in pulmonary capillary arterial and mixed venous blood respectively. From the value of $C_{\bar{c}CO_2}$ the corresponding P_{CO_2} was estimated from the nomogram given by Dill *et al.* (9). This value for $P_{\bar{c}CO_2}$ was considered to be a more correct estimate of P_{ACO_2}. The only case (no. 18 a and b) of the present series, in which a correction was thought to be necessary had a shunt of about 20 per cent of cardiac output. The magnitude of the correction, corresponding to this shunt, was 1 mm Hg or of about the same size as the error of the method used for determining $P_{\bar{c}CO_2}$ (± 1 mm Hg).

The analytical methods were the same as those reported in the first chapter except the determination of the arterial oxygen tension (P_{aO_2}). In the present investigation this determination was made with a Clark electrode (8) using mylar membrane (31). The measurement was made in a Severinghaus stainless steel cuvette (33) kept at constant temperature in Yellow Springs Company water bath[1] with an I. L. Meter[2] immediately after withdrawal of the blood. The error of a single determination of P_{O_2} at high range of oxygen tensions (500—700 mm Hg) was estimated from duplicate readings on equilibrated blood to be ± 1.0 %. In the low range (O_2 tensions 60—100 mm Hg) the error was estimated to be ± 0.5 %.

The determination of *the pulmonary capillary blood volume* (V_C) and *the membrane diffusion capacity* (D_M) was made according to the method of Roughton, Forster *et al.* (14 15 34) as modified by Bates *et al.* (2). By measuring the pulmonary diffusion capacity for monoxide (D_{LCO}) at two different alveolar oxygen tensions these

[1] Commercial production model built by Yellow Springs Instrument Company Yellow Springs, Ohio.

[2] Instrumentation Laboratory Inc., Boston, Massachusetts

authors calculated D_M and V_C by solving the equation

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta V_C} \qquad (1)$$

with the aid of the two determined values of $D_{L_{CO}}$. *In this equation $1/D_{L_{CO}}$, $1/D_M$ and* $1/\theta_{V_C}$ are analogue to the total resistance of the lungs to diffusion, the pulmonary membrane resistance and the intracapillary resistance, respectively. θ is a velocity constant related to the rate of uptake of CO by blood *in vitro* and $\frac{1}{\theta}$ is linearly related to the mean capillary oxygen tension. The parameter $\frac{1}{\theta}$ is calculated from the formula

$$\frac{1}{\theta} = 0.0057 \times \bar{P}_{O_2} + 0.75 \qquad (2)$$

given by Roughton and Forster (34). This equation is based on the assumption that λ (the ratio of permeability of the red blood cell membrane to the red cell interior) = 2.5. The mean capillary oxygen tension ($\bar{P}_{c_{O_2}}$) was calculated by the method described by Linderholm (28). The values for θ given by Roughton and Forster are average values calculated on the basis of a CO capacity of 20 ml. per 100 ml. blood *(14.9 g Hb/100 ml.). If the CO capacity is* divergent from this value, a correction should be made in the calculation of V_C (5, 29) since θ is proportional to this capacity according to the equation

$$V_C(\text{corrected}) = V_C \times 14.9/\text{Hb gr } \% \quad (3)$$

In the present study $D_{L_{CO}}$ was measured at two different alveolar oxygen tensions, *one high, 60 or 100 per cent oxygen, and one* low, air. All determinations were made at rest with the subject in recumbent position. The values for V_C given in table III are corrected according to eq. 3.

Normal values for D_M and V_C earlier presented in literature (2, 5, 12, 26, 29) are given in table I.

Table I. Normal values for D_M and V_C.

Reference	Method	Number of subjects	Body position	V_C ml	D_M ml STPD/min/mm Hg
1. Roughton and Forster 1957	Single breath rest		sitting	[illegible]	[illegible]
	Steady state rest		sitting	[illegible]	[illegible]
2. McNeill, Rankin and Forster 1958	Single-breath rest		sitting	[illegible]	[illegible]
3. Lewis et al. 1958	Single-breath rest		recumbent sitting	[illegible]	[illegible]
	Rebreathing rest		recumbent sitting	[illegible]	[illegible]
4. [illegible] et al. 1960	Steady state slight exercise	below the age of 35	lying	[illegible]	[illegible]
		above the age of 35	sitting	[illegible]	[illegible]
5. [illegible] et al. 1960	Single breath rest		sitting	47	[illegible]

The data are given as means with range in brackets.

Procedure

The subject was first breathing pure oxygen from a demand valve, in order to estimate the size of the anatomical shunt, the expired gas volume being collected in a rubber bag. Simultaneously the nitrogen wash-out curve was recorded, according to the method described in the first chapter. As soon as the nitrogen concentration had reached the 2 per cent level, the collection of expired gas was interrupted. When the nitrogen concentration had reached its lowest value, the subject was asked to breath out as deep as possible. This procedure was repeated with some minutes interval, until no increase of the nitrogen end tidal level could be observed. At this time arterial blood was drawn for analysis of oxygen tension. By this procedure it was possible to decide with reasonable certainty when the oxygen wash-in was complete and any possible leakage in the closed system could be discovered immediately

The subject was then breathing 60 (or in some cases 100) per cent oxygen during a period corresponding to the nitrogen wash-out time (in these cases about 4 minutes) At the end of this time he was connected to the inspiratory bag, which contained the same oxygen concentration he had been breathing, with the addition of approximately 0.20 per cent CO The expired gas was collected in another bag during period of 5 minutes. In the middle of this period sample of arterial blood was drawn for the determination of P_{CO_2} P_{O_2} and P_{aCO} After 10 minutes of rest, the subject was switched into a mixture of air containing about 0.12 per cent CO the sequence of events being timed as before. The CO_2–O_2 and CO-concentrations of inspired and [illegible] ined as described in Chapter I. The relatively high inspired CO concentration was used during the 100 per cent oxygen determination to lower the proportionate effect of "back pressure" of CO in relation to alveolar CO concentration (2) pH, P_{CO_2} and standard bicarbonate were determined immediately after the sample of arterial blood was drawn with the micro-Astrup technique (see chapter 1)

Results

The results are shown in tables II and III and in *fig.* 11 In table II anthropometric data in the eight subjects studied, and some results of resting pulmonary function tests are presented. The average age of the group was 33 3 (range 19—50)

The static lung volumes are represented by the observed values for the *vital capacity* and *total capacity* They were found to be slightly reduced, the reduction being of about the same magnitude as was observed in the earlier material of "atypical" pneumonias (table IV chapter 1) The *quotient residual volume total capacity* averaged 27 5 or 112 % of predicted. This quotient was somewhat high in 3 cases (nos. 17 18 and 20) but their vital capacities were also somewhat low

The dynamic spirogram was shown to be normal or almost normal except in 2 cases (nos. 18 and 20) who had a somewhat low *FEV %* (86 and 83 per cent, respectively of predicted normal value) and *maximal mid expiratory flows reduced to about half of* the predicted value.

The wash-out index was on an average 7 49 (range 6.45—8.70) or within normal limits in all cases.

Alveolar ventilation as indicated by P_{aCO_2} shown in *table III*, was within normal limits in all cases of the group and the values for

authors calculated D_M and V_C by solving the equation

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta V_C} \qquad (1)$$

with the aid of the two determined values of $D_{L_{CO}}$. In this equation $1/D_{L_{CO}}$, $1/D_M$ and $1/\theta_{V_C}$ are analogue to the total resistance of the lungs to diffusion, the pulmonary membrane resistance and the intracapillary resistance, respectively. θ is a velocity constant related to the rate of uptake of CO by blood *in vitro* and $\frac{1}{\theta}$ is linearly related to the mean capillary oxygen tension. The parameter $\frac{1}{\theta}$ is calculated from the formula

$$\frac{1}{\theta} = 0.0057 \times \bar{P}_{c_{O_2}} + 0.73 \qquad (2)$$

given by Roughton and Forster (34). This equation is based on the assumption that λ (the ratio of permeability of the red blood cell membrane to the red cell interior) = 2.5. The mean capillary oxygen tension ($\bar{P}_{c_{O_2}}$) was calculated by the method described by Linderholm (28). The values for θ given by Roughton and Forster are average values calculated on the basis of a CO capacity of 20 ml. per 100 ml. blood (14.9 g Hb/100 ml.). If the CO capacity is divergent from this value, a correction should be made in the calculation of V_C (5,29) since θ is proportional to this capacity according to the equation

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Normal values for D_M and V_C earlier presented in literature (2, 5, 12, 26, 29) are given in table I.

Table I. Normal values for D_M and V_C.

Reference	Method	Number of subjects	Body position	D_M	V_C ml STPD/min/mm Hg
Roughton and Forster	single-breath rest		sitting	75 ([illegible])	[illegible] ([illegible])
	Steady state rest		sitting	[illegible] ([illegible])	[illegible] ([illegible])
McNeill [illegible] and [illegible]	[illegible] breath [illegible]		sitting	[illegible]	[illegible]
Lewis et al. [illegible]	single-breath rest		recumbent / sitting	[illegible]	[illegible]
	[illegible]		recumbent / sitting	[illegible]	[illegible]
Bates et al. [illegible]	Steady state light exercise	below the age of [illegible]	sitting	[illegible] ([illegible])	[illegible]
		above the age of 35	sitting	[illegible] ([illegible])	[illegible] ([illegible])
[illegible] et al. [illegible]	Single-breath rest		sitting	[illegible] ([illegible])	([illegible])

The data are given as mean with range in brackets.

Procedure

The subject was first breathing pure oxygen from a demand valve, in order to estimate the size of the anatomical shunt, the expired gas volume being collected in a rubber bag. Simultaneously the nitrogen wash-out curve was recorded, according to the method described in the first chapter. As soon as the nitrogen concentration had reached the 2 per cent level, the collection of expired gas was interrupted. When the nitrogen concentration had reached its lowest value, the subject was asked to breath out as deep as possible. This procedure was repeated with some minutes interval, until no increase of the nitrogen end tidal level could be observed. At this time arterial blood was drawn for analysis of oxygen tension. By this procedure it was possible to decide with reasonable certainty when the oxygen wash-in was complete and any possible leakage in the closed system could be discovered immediately.

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Results

The results are shown in tables II and III and in fig. 11. In table II anthropometric data in the eight subjects studied, and some results of resting pulmonary function tests are presented. The average age of the group was 33.3 (range 19—50).

The static lung volumes are represented by the observed values for the *vital capacity* and *total capacity*. They were found to be slightly reduced, the reduction being of about the same magnitude as was observed in the earlier material of atypical pneumonias (table IV chapter I). The *quotient residual volume total capacity* averaged 27.5 or 112 % of predicted. This quotient was somewhat high in 3 cases (nos. 17, 18 and 20) but their vital capacities were also somewhat low.

The dynamic spirogram was shown to be normal or almost normal except in 2 cases (nos. 18 and 20) who had a somewhat low FEV % (86 and 83 per cent, respectively of predicted normal value) and *maximal mid expiratory flows* reduced to about half of the predicted value.

The wash-out index was on an average 7.49 (range 6.45—8.70) or within normal limits in all cases.

Alveolar ventilation as indicated by P_{aCO_2} shown in table III, was within normal limits in all cases of the group and the values for

Table II Anthropometric data and results of pulmonary function studies in 8 subjects 1—26 weeks after the "atypical" pneumonia

Case no	Sex	Age	Height	Weight	VC		TC		RV/TC 100		FEV%		MMF		$\frac{V_E}{FRC}$ ($T_{F_{N_2}}$ 1%)
					Obs. l.	% of pred.	Obs. l.	% of pred.	Obs. l.	% of pred.	Obs. l	% of pred.	Obs. l/min.	% of pred.	
13	F	[illegible]	161	54.0	2.[illegible]	91	4.[illegible]	83	[illegible]	1[illegible]	[illegible]	1[illegible]	2.2	[illegible]	7 40
14	F	[illegible]	167	61.8	3 [illegible]	87	5.52	107	30	111	[illegible]	[illegible]	2.[illegible]	[illegible]	[illegible]
16	F	41	171	63 7	3 30	[illegible]	4.[illegible]	93	[illegible]	100	82	87	3.30	87	7.[illegible]
17	F	19	16[illegible]	40 6	2.[illegible]	[illegible]	4 16	[illegible]	36	114	[illegible]	83	2.23	41	[illegible]
18a	F	41	1[illegible]	63.7	3.[illegible]		4.[illegible]		36		73		1.13		9 17
18b	F	41	16[illegible]	62.0	2.97	64	4.63	82	[illegible]	1[illegible]	73	[illegible]	1 37	[illegible]	8.70
18c	F	41	1[illegible]	63 8	2.70		5.71		34		71		2.[illegible]		7 30
19	F	[illegible]	16[illegible]	61	2.84	10[illegible]	4 34	[illegible]	18	[illegible]		104	8.[illegible]	136	8.[illegible]
20	M	[illegible]	179	78.0	2.84	63	5.20	[illegible]	38	200	72	[illegible]	2.47	[illegible]	8.18
21	M	[illegible]	174	77	6 07	133	7 [illegible]	133	23	70	78	100	3.71	119	6 [illegible]
Mean		[illegible]	169 6	62.4	3.[illegible]	[illegible] 4	5.0[illegible]	94.3	27 8	113	[illegible]	[illegible]	2.14	[illegible]	7 [illegible]
Range		19–[illegible]	161 179	40 6–78.0	2.[illegible]–6 07	[illegible]–133	4.16–7 93	[illegible]–133	18 38	[illegible]–200	72–84	[illegible]–108	1 37–8.[illegible]	[illegible]–136	[illegible]–8.70

VC vital capacity TC total lung capacity FEV% forced expiratory volume in one second in per cent of forced vital capacity

MMF maximum midexpiratory flow $\frac{V_E}{FRC}$ ($T_{F_{N_2}}$ 1%) pulmonary mixing index

The values of case 18a and c not included in the mean values and ranges of the group.

P_{ACO_2} are in close agreement with those found in the atypical pneumonia group earlier described (Table VI chapter I) P_{aO_2} during air breathing was on an average 85 mm Hg (range 64—102) or slightly lower than in a normal material reported earlier (18) One case (no 18) had values lower than twice S.D of this series in the two first investigations (no 18 a and b) but was within normal limits in the third investigation (18 c) One case (no 20) had a value lower than once S D of the same material but otherwise P_{aO_2} was within normal limits.

The diffusion capacity ($D_{L_{CO}}$) *capillary blood volume* (V_C) and *membrane diffusion capacity* (D_M) *at rest*

$D_{L_{CO}}$ measured at an alveolar oxygen tension of about 110 mm Hg (air breathing) was on an average 16.49 ml/min./mm Hg (range 7 50—24.76) or 70 % of the predicted normal value (range 37 5—136.8) $D_{L_{CO}}$ at an alveolar oxygen tension of about 360 mm Hg (breathing 60 per cent oxygen) averaged 10 48 ml/min./mm Hg (range 5 23—19 0) and at an alveolar oxygen tension of about 650 mm Hg (breathing pure oxygen) 7 60 ml/min./mm Hg. D_M calculated from the $D_{L_{CO}}$ values obtained at the two alveolar oxygen tension levels, was reduced in all cases of the group except one (case no. 14) the average value being 24 34 ml/min./mm Hg (range 14.1—34 5) Also in relation to ventilated lung volume (midcapacity) a reduction of D_M can be seen. The values of D_M/MC found in these subjects varied between 6.14 and 10 93 whereas the normal range is from 9—17 approximately

The average value of V_C was 87 5 ml (range 23 6—200 ml) Five cases (nos. 13 14, 17 18 and 20) had values below the approximate normal range of 68—200 ml. reported by Bates *et al* (2) It should be observed that V_C in absolute terms is subject to a considerable variation. The possible

Table III Ventilation, pulmonary capillary blood volume (V_C), membrane diffusing component (D_M) and related data in 8 subjects in the course following "atypical" pneumonia

Case no.	F_{IO_2}	$\dot{V}_E$ STPD/min	V_D/V_T	$\dot{V}_{O_2}$ ml/min STPD	$P_{A_{O_2}}$ mm Hg	$P_{a_{O_2}}$ mm Hg	$P_{a_{CO_2}}$ mm Hg	$D_{L_{CO}}$ ml STPD/min/mm Hg, breathing air: Obs.	$D_{L_{CO}}$ breathing air: % pred.	$D_{L_{CO}}$ ml STPD/min/mm Hg breathing O_2	[illegible]	D_M ml STPD/min/mm Hg	$D_{L_{O_2}}$ breathing air: Obs.	$D_{L_{O_2}}$ breathing air: % of pred.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] range	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] range	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]			[illegible]									
[illegible]											[illegible]	[illegible]			[illegible]	[illegible]		[illegible]	

[illegible]

Table II Anthropometric data and results of pulmonary function studies in 8 subjects 1—26 weeks after the "atypical" pneumonia

Case no	Sex	Age	Height	Weight	VC Obs. l.	VC % of pred.	TC Obs. l.	TC % of pred.	RV/TC × 100 Obs.	RV/TC × 100 % of pred.	FEV% Obs.	FEV% % of pred.	MMF Obs. l/sec.	MMF % of pred.	$\frac{V_F}{FRC}$ ($T_{E_{N_2}}$) %
13	F	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4.[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	7.[illegible]
[illegible]	F	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	107	[illegible]	111	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	F	41	171	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	67	7.[illegible]
17	F	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	124	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
18a	F	41	[illegible]	[illegible]	[illegible]		4.[illegible]		[illegible]		[illegible]		[illegible]		[illegible]
18b	F	41	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
18c	F	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	–	[illegible]		[illegible]		[illegible]		7.[illegible]
[illegible]	F	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	104	[illegible]	[illegible]	[illegible]
20	M	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
21	M	[illegible]	174	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	119	[illegible]
Mean		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Range		[illegible]	161—179	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

VC vital capacity TC total lung capacity FEV% forced expiratory volume in one second in per cent of forced vital capacity

MMF maximum midexpiratory flow $\frac{V_F}{FRC}$ ($T_{E_{N_2}}$ [illegible]) pulmonary mixing index

The values of case 18a and [illegible] not included in the mean values and ranges of the group.

$P_{A_{CO_2}}$ are in close agreement with those found in the "atypical" pneumonia group earlier described. (Table VI chapter I) $P_{a_{O_2}}$ during air-breathing was on an average 85 mm Hg (range 64—102) or slightly lower than in a normal material reported earlier (18) One case (no 18) had values lower than twice S.D of this series in the two first investigations (no. 18 a and b) but was within normal limits in the third investigation (18 c) One case (no 20) had a value lower than once S.D of the same material, but otherwise $P_{a_{O_2}}$ was within normal limits

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The average value of V_C was 87 5 ml (range 23 6—200 ml) Five cases (nos 13 14, 17 18 and 20) had values below the approximate normal range of 68—200 ml. reported by Bates et al (2) It should be observed that V_C in absolute terms is subject to a considerable variation. The possible

18) was shown to have a shunt amounting to 22 per cent of cardiac out-put at the first investigation and 20.3 per cent at the second one. In this case the alveolar carbon dioxide calculated on the assumption that $P_{aCO_2} \approx P_{ACO_2}$ was corrected according to the above method.

In fig. 11 the relationship between $\frac{1}{D_L}$ and mean capillary oxygen tension ($\bar{P}_{aO_2}$) in the individual cases of the group is shown.

In fig. 12 D_M V_C, TC and $\frac{Q_{sh}}{Q_T}$ expressed in per cent of predicted values found in case no. 18 during the time of observation, are shown. The highly reduced membrane dif fusion capacity and capillary blood volume

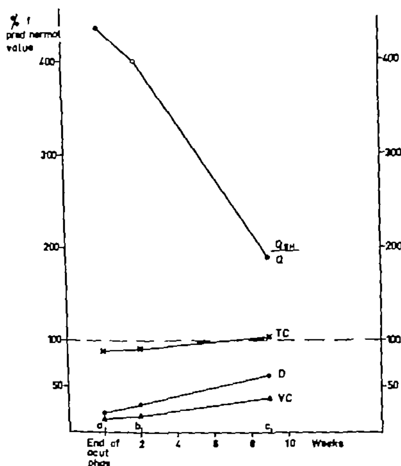


Fig. 12 Pulmonary membrane diffusion capacity (D_M) pulmonary capillary blood volume (V_C) total lung capacity (TC) and venous admixture during oxygen breathing ($\dot{Q}_{sh}/\dot{Q}_T$) in per cent of predicted normal values in case no. 18 at repeated investigations (a, b and) after the end of the acute stage of pneumonia. (see text)

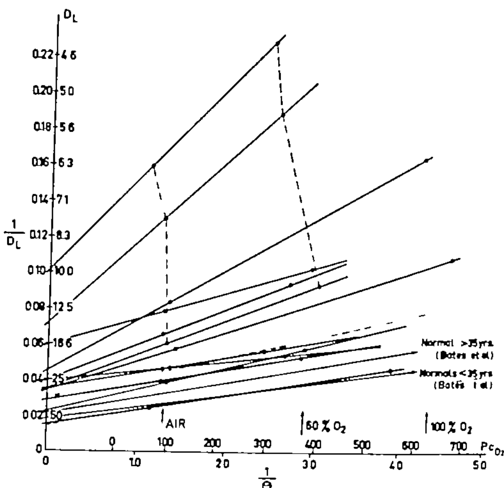


Fig 11 Relation between $\frac{1}{D_L}$ (mm Hg×min/ml) (ordinate) and mean capillary oxygen tension, $\bar{P}_{O_2}$ (mm Hg) and corresponding values of $\frac{1}{\Theta}$ (min/mm Hg×ml) (abscissa) Dotted lines indicate range of variation in 14 healthy subjects according to Bates *et al* (2) Filled circles represent the present material. In comparison, values for two normal cases (open circles) investigated by the author are given. In one case (no 18) values for three different occasions (see text) are connected with broken lines.

causes of this will be discussed later V_C in relation to mid-capacity was on an average 27 85 ml (range 10 78—54 86) In four cases (nos 13 15 18 and 20) this value was reduced below the lower normal limit, which is about 24—56 ml. The quotient resistance cell/resistance membrane in % averaged 53 40 (range 17 9—88.0) or about half the approximate average normal value of 129 7 % given by Roughton and Forster (34) indicating that the membrane resistance in most cases of the material was greater than normal.

The *anatomical shunt* averaged 8.39 per cent of cardiac out put (range 4.1—20 3) which is of about the same order as in the atypical pneumonia group in the first chapter. One case in the present material (no.

oxygen tension (P_{aO_2}) (27). Fortunately this error seems to be of relatively small significance (29).

In the present series D_M was found to be below the expected normal value in most cases. D_M is presumably influenced by changes in 1) the surface area of functioning capillaries in contact with functioning alveoli, of 2) the thickness of the alveolo-capillary membrane and 3) the physical and chemical properties of this membrane. A reduction of the membrane diffusion component may consequently be caused by a decrease of the functioning diffusion area, an increased thickness of the pulmonary membrane and/or a change of its properties. The anatomical shunts of moderate size found in most cases of this series may indicate, that areas with non-ventilated alveoli still exist in the affected lung parenchyma, even after normalization of the x-ray picture. D_M was, however, found to be decreased *not only* in absolute terms but also in relation to lung-volume (midcapacity) which may indicate, that changes of the pulmonary membrane itself can have been of significance. This is supported by the observation that the ratio intracapillary resistance/membrane resistance was more or less decreased.

The capillary blood volume was found to vary considerably but was within approximately normal limits (29) in about half of the subjects studied. A decrease of both V_C and D_M may be expected in cases with an increased anatomical shunt. In case no. 18 (fig. 12) these conditions are fairly well demonstrated. No simple relation was, however, found between the observed reduction of V (or D_M) and the size of the shunt, as would have been expected, if other possible factors influencing the capillary bed were of little importance. V_C as well as D_M may also be reduced as a result of capillary obliteration or destruction caused by lesions originating in the acute infectious phase, and, thus, to some extent, contribute to the observed decrease in V_C. A third possibility which seems to be of importance although not yet studied in detail, is the influence of changes of the central blood volume on the capillary bed due to lowering of the venous tone in the systemic circulation in subjects with a tendency to orthostatic reactions. Such reactions, although not so pronounced as, for example, in patients with sarcoidosis (19) have been observed in convalescents after infectious diseases (see chapter I). It is at present, impossible to draw any conclusions about the quantitative relations between these factors. However, it may be a reasonable assumption that all these factors could contribute to the observed reduction of capillary blood volume in some of the cases.

Summary

Pulmonary diffusion capacity ($D_{L_{CO}}$), membrane diffusion capacity (D_M) and pulmonary capillary blood volume (V_C) have been studied in 8 subjects at various times in the course following the acute phase of atypical pneumonia. The x-ray picture was, at the time of investigation, in most cases normalized or almost normalized.

Alveolar ventilation and distribution of inspired gas was within normal limits in all cases.

Anatomical shunts ranging from 4 to 22 per cent of cardiac output were found.

The membrane diffusion capacity (D_M) was decreased in most cases, both in absolute terms and in relation to the midcapacity of the lungs.

The capillary blood volume (V_C) was found to vary considerably being either normal or reduced.

found at the first investigation, shows a marked increase and the anatomical shunt has decreased more than 10 per cent of cardiac output during the observation period, but there is still a demonstrable impairment of the lung function at the last investigation. From table III it may be seen that the arterial oxygen tension while breathing air was significantly low at the first two investigations (62 and 64 mm Hg, respectively) but almost normalized at the third one (87 mm Hg)

Discussion

Values for D_M obtained with the steady state technique (11) are generally found to be lower than D_M determined with the single breath technique (13 22, 23) (table I) V_C, on the other side, is found to be higher when determined with the steady state method. These differences may be explained by uneven distribution of different functions within the lungs, depending on which of the two methods is used. Thus during the single breath holding measurements alterations in pumonary blood flow may be produced, resulting in secondary changes in D_L (6 14) Variations in the distribution of pulmonary diffusion capacity in relation to alveolar volume may at least in part, influence the results obtained by the single breath technique (6) The steady state method is dependent on the assumption that $P_{A_{CO_2}} = P_{a_{CO_2}}$ (32) which is not true when large shunts are present within the lungs, and is also influenced by the uniformity of distribution of pulmonary diffusion capacity in relation to alveolar ventilation (12)

In the present study the determinations of D_L D_M and V_C were made with the steady state method at rest in supine position, and should consequently be compared with normal values obtained with the same technique. Such values for D_M and V_C in seven healthy subjects, presented by Lewis *et al* (26) using similar technique, were on an average 51 ml/min./mm Hg and 135 ml, respectively Consequently these values could have been used as normal values when analysing the results obtained in the present material. However, as can be seen in table I the average normal values of D_M and V_C presented by Bates *et al* (2) also using the steady state technique, are in close agreement with those presented by Lewis *et al* although the subjects were studied during slight exercise in sitting position. As the series of Bates *et al* further included two groups of normal individuals (seven normal subjects below and seven above the age of 35) and as the results reported seemed to be sufficiently stable and reliable to permit comparison to be made between normal subjects and patients this was judged to be the most suitable of the earlier presented normal materials and, thus compared with in the present study

The determinations of D_M and V_C are based on certain assumptions or approximations, to some extent decreasing their validity 1 The values for θ, the rate of CO uptake by the red cells at various oxygen tensions, were determined *in vitro* by Roughton and Forster (34) from two extreme values for red cell membrane permeabilities, and the two sets of values for D_M and V_C thus obtained, were averaged. McNeill *et al* (29) and others (2 5) used values for θ corresponding to an average value of $\lambda = 2.5$ and calculated only one set of values for D_M and V_C The same value for λ was used in the calculations on the present series The true value of λ and consequently of θ *in vivo* is still uncertain. 2 The approximations made in the calculations of mean capillary

oxygen tension (P_{CO_2}) (27). Fortunately this error seems to be of relatively small significance (29).

In the present series D_M was found to be below the expected normal value in most cases. D_M is presumably influenced by changes in 1) the surface area of functioning capillaries in contact with functioning alveoli, of 2) the thickness of the alveolo-capillary membrane and 3) the physical and chemical properties of this membrane. A reduction of the membrane diffusion component may consequently be caused by a decrease of the functioning diffusion area, an increased thickness of the pulmonary membrane and/or change of its properties. The anatomical shunts of moderate size found in most cases of this series may indicate, that areas with non-ventilated alveoli still exist in the affected lung parenchyma, even after normalisation of the x-ray picture. D_M was, however, found to be decreased not only in absolute terms but also in relation to lung volume (midcapacity) which may indicate, that changes of the pulmonary membrane itself can have been of significance. This is supported by the observation that the ratio intracapillary resistance/membrane resistance was more or less decreased.

The capillary blood volume was found to vary considerably but was within approximately normal limits (29) in about half of the subjects studied. A decrease of both V_C and D_M may be expected in cases with an increased anatomical shunt. In case no. 18 (fig. 12) these conditions are fairly well demonstrated. No simple relation was, however found between the observed reduction of V_C (or D_M) and the size of the shunt, as would have been expected, if other possible factors influencing the capillary bed were of little importance. V_C as well as D_M may also be reduced as a result of capillary obliteration or destruction caused by lesions originating in the acute infectious phase, and, thus, to some extent, contribute to the observed decrease in V_C. A third possibility which seems to be of importance although not yet studied in detail, is the influence of changes of the central blood volume on the capillary bed due to lowering of the venous tone in the systemic circulation in subjects with a tendency to orthostatic reactions. Such reactions, although not so pronounced as, for example, in patients with sarcoidosis (19) have been observed in convalescents after infectious diseases (see chapter I). It is, at present, impossible to draw any conclusions about the quantitative relations between these factors. However it may be a reasonable assumption that all these factors could contribute to the observed reduction of capillary blood volume in some of the cases.

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CHAPTER III

A follow-up study on the cardio-pulmonary function in the course following atypical "pneumonia

In the second chapter one case (no. 18) was studied on three occasions during a period of about two months after the end of the acute infectious phase. The results obtained in this case indicate a fairly rapid improvement of the pulmonary function, though this was, however, by no means nor realized at the end of the observation time. Another case in this series, who had suffered from psittacosis, was investigated about one year after the end of the acute pneumonia and was shown still to have some impairment of the lung function.

The results in these separate cases give no definite answer to the question about the evolution of the lung function in the course following atypical pneumonia. Consequently it may be of interest to present data from a follow-up study in group of subjects with the clinical diagnosis of atypical pneumonia.

Material and Methods

The group consisted of 9 subjects, 3 males and 6 females. All of them were taken from the series presented in the first chapter in which further details about the acute stage of illness, x-ray picture etc. are given. The subjects were taken to a second investigation about six months after the first one, the somewhat different time intervals between the two investigations in the individual cases being caused by practical circumstances. The subjects were carefully asked for new respiratory infections and for other symptoms from the respiratory tract during the period between the two investigations. One of the cases (no. 11) was found to have had a clinically demonstrable respiratory infection 2 months after the first investigation. At that time she had symptoms of a new pneumonia with fever hoarseness and unproductive cough and was admitted to the Epidemic Hospital in Stockholm. The x ray showed streaked infiltrations of pneumonic type in the right middle lobe. The cold hemagglutination was found to be 1:8 at admittance and 1 32 one week later. The clinical diagnosis was pneumonia primaria atypica recidivans. During convalescence she had marked fatigue and more or less pronounced cough, which still embarrassed her at the time of the second investigation.

Most of the other cases of the group complained of more or less pronounced fatigue and cough and even, to some extent, of effort dyspnea.

The *x-ray picture* at the time of the second *investigation* was in most cases normal or almost normal. One case (no. 13) had a small calcified tuberculoma in the

right upper lobe, which had been observed already at the first investigation but no lesions could be seen in the lung parenchyma.

In the above mentioned case (no 11) *slight radiating densities could still be seen*, probably originating from the second pneumonia. Otherwise the x ray picture was quite unchanged *in comparison to that at the* first investigation.

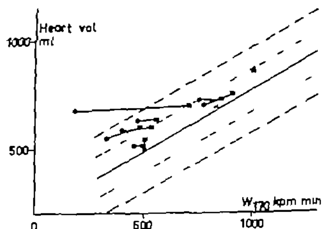
The *methods and calculations* used in this investigation were the same as described in the first chapter (1 3 7 9 10 11 12, 13 16 17 18 19 23 24 25) The oxygen tension determinations however were made with the equipment described in the second chapter (8, 21 22)

Results

The results obtained in the second investigation are shown in table I—III and in fig 13—15 The corresponding values from the first investigation are given within parentheses. In table I the anthropometric characteristics of the 9 subjects studied, are shown together with results of circulatory studies. The average age of the group was 38 (range 19—61)

Heart volume in prone position was on an average 660 ml or approximately within normal limits in relation to age and weight (6) The mean difference between the two *investigations was* + *50 ml, which is not* statistically significant.

Working capacity W_{170} sitting, averaged 667 7 kpm/min. The corresponding value at the first test occasion was 511 1 kpm/min. the increase being statistically highly significant (p=***) The individual values W_{170}, determined at the two investigations, have been plotted against the corresponding values earlier reported by Holmgren *et al* (14) (*fig* 13) From this figure it can be seen that W_{170} in most cases has increased considerably in relation to heart volume and that the individual values have thus moved closer to the regression line. All cases are, however still to the left of this line



lume ml, (ordinate) in relation pulse rate of 170 beats/min (absc[illegible] the time of the fill[illegible] the second one about a month later (filled squares) Corresponding individual values are connected (see text)

Table 1 Some anthropometric data [illegible] 9 subject at second [illegible] investigation [illegible] the [illegible] following atypical [illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
																[illegible]
		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]				[illegible]
		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]				[illegible]
		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]				[illegible]
		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]				
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[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]				[illegible]
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[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	

W_{75} [illegible]

[illegible]

Orthostatic test Most cases of the group showed only moderate increase of the pulse rate in standing, the average value being 87 0 beats/min The corresponding value at the first investigation was 101 0 beats/min. The difference is not statistically significant but might indicate that the orthostatic reactions, which even at the first investigation were found to be rather moderate had almost disappeared at the second one

Influence of posture on W_{170} was studied in 5 cases of the group The difference between pulse rate sitting and in supine position, which was found to be statistically probably significant (12 3 beats/min.) at the first investigation, had decreased to only 0.3 beats/min. at the second one Thus it may be said, that orthostatic pulse reactions dur ing work at the second investigation were of little importance

Pulmonary Function

The static lung volumes are represented by the observed values of the *vital capacity*, *total capacity* and the *quotient residual volume/total capacity* (table II) Both vital capacity and total capacity had increased, the former from 85 to 91 per cent of predicted value and the latter from 87 to 96 per cent of predicted value (fig. 14) In relation to the corresponding values of the non-pulmonary" group (presented in the first chapter table V) they are however, still slightly reduced at the second investigation. The observed difference in VC between the two investigations was not statistically significant but the corresponding difference in TC was probably significant (p = *) The differences in VC and TC found between the present group and the above mentioned non-pulmonary group were statistically significant

Table II Lung volumes 1 BTPS mechanics of breathing an nitrogen wash-out index in 9 subjects at a second investigation in the course following atypical" pneumonia. The corresponding values from the first investigation in brackets

Case No.	VC Obs	VC % of pred.	TC Obs. l	TC % of pred.	RV/TC Obs. %	RV/TC % of pred	MBC Obs l/m.	MBC % of pred	FEV % Obs %	FEV % % of pred.	MMF Obs. l/sec	MMF % of pred	Nitrogen wash-out index $\frac{VE}{FRC}$ ($T_{E_{2}}$ 2.5)
[illegible]	2.44	[illegible]	[illegible]	[illegible]	[illegible]	103	103	130	64	[illegible]	4.[illegible]	[illegible]	[illegible]
[illegible]	3 [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	134	97	73	[illegible]	[illegible]	[illegible]	[illegible]
7 ♀	[illegible]	[illegible]	4.[illegible]	[illegible]	27		103	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	17	7 [illegible]	113	[illegible]	[illegible]	[illegible]	97	71	81	[illegible]	73	[illegible]
1 ♀	[illegible]	[illegible]	4.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	79	[illegible]	13	79	[illegible]
12 ♀	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	87	[illegible]
13 ♀	[illegible]	[illegible]	4.[illegible]	[illegible]	[illegible]	[illegible]	112	85	[illegible]	100	34	[illegible]	[illegible]
14 ♀	2.[illegible]	87	[illegible]	87	[illegible]	11	97	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
18 ♀	[illegible]	[illegible]	4.[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	11	[illegible]	97	[illegible]	97	[illegible]
♂ M	4.[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	97	97	[illegible]	77	97	[illegible]	[illegible]	[illegible]
	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	(72.7)	([illegible])	([illegible])	([illegible])	
♀ M	[illegible]	[illegible]	4.[illegible]	[illegible]	[illegible]	11	11	[illegible]	[illegible]	97	[illegible]	[illegible]	[illegible]
	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	
Group M	[illegible]	91	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	97	[illegible]	[illegible]	[illegible]
	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])	([illegible])
M of "non-pulm. group"		109		[illegible]		[illegible]						[illegible]	[illegible]

VC vital capacity TC total lung capacity RV residual volume, MBC maximum breathing capacity FEV % forced expiratory volume in one second in per cent of forced vital capacity MMF maximum midexpiratory flow
The corresponding values from the first investigation in brackets

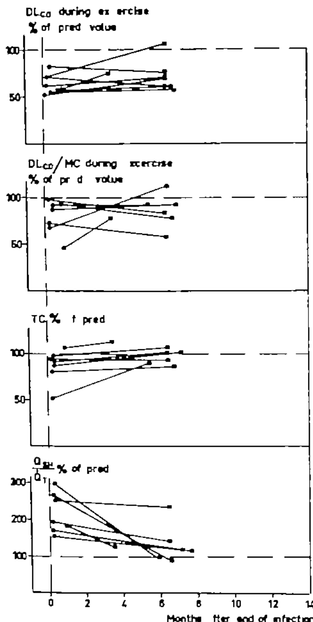


Fig. 14. D_{LCO} ml STPD/min/mm Hg absolutely and in relation to pulmonary midcapacity (MC) total lung capacity (TC) and venous admixture during oxygen breathing ($\dot{Q}_{sh}/\dot{Q}_T$) in per cent of predicted normal values at the time for the two investigations. Filled circles represent values obtained at first investigation, filled squares those obtained at the second one.

Table III Ventilation diffusion acapacity and related values in 9 subjects at two test

Case no.	Work load kpm/min.		V_D/V_T		V_{O_2} ml/min STPD		$P_{A_{O_2}}$ mm Hg		$P_{a_{O_2}}$ mm Hg		$P_{a_{CO_2}}$ mm Hg /		$D_{L_{CO}}$ ml STPD/min/mm Hg	
	I	II	I	II	I	II	I	II	I	II	I	II	I Obs.	II % of pred.
2	rest 600	rest 600	0 [illegible] 0 [illegible]	0 [illegible] 0 10	273 1364	270 1026	10[illegible] 10[illegible]	100 110	7[illegible] [illegible]	[illegible] [illegible]	[illegible] 40	[illegible] 37	[illegible] 07 22.40	77 90
6	rest 400	rest 400	0 [illegible] 0 21	81 0 22	[illegible] 1100	271 1640	114 117	10[illegible] 118	70 [illegible]	78 67	[illegible] [illegible]	37 [illegible]	[illegible] 16 [illegible]	[illegible] [illegible]
7	rest 100	rest 400	[illegible] 0 27	0 41 0.20	100 1207	190 1278	111 [illegible]	101 112	[illegible] [illegible]	[illegible] [illegible]	[illegible] [illegible]	34 [illegible]	10 [illegible] [illegible]	34 [illegible]
	rest 400	400 800	0 [illegible] 0.11	16 0 10	[illegible] 1434	10[illegible] 100[illegible]	107 10[illegible]	105 112	[illegible] 64	[illegible] [illegible]	34 30	41 38	17 [illegible] [illegible] 47	[illegible] [illegible]
11	rest 150	rest 400	0 33 0 [illegible]	0 33 0 [illegible]	184 [illegible]	217 1041	110 11	112 113	[illegible] [illegible]	70 [illegible]	[illegible] [illegible]	[illegible] [illegible]	[illegible] 13 [illegible]	[illegible] [illegible]
12	 300	rest 400	 0 [illegible]	0 42 0 37	 [illegible]	841 1004	 112	101 [illegible]	 [illegible]	7[illegible] [illegible]	 [illegible]	38 42	 [illegible]	 [illegible]
13	rest 300	rest 400	0 34 32	0 44 0 1	[illegible] [illegible]	131 [illegible]	111 107	111 10[illegible]	[illegible] 64	[illegible] 100	33 40	[illegible] 30	7.97 13.63	[illegible] [illegible]
14	rest 400	rest 600	0 [illegible] [illegible]	43 0 1	[illegible] 1[illegible]	[illegible] 1313	110 11	[illegible] 112	70 10[illegible]	100 10[illegible]	[illegible] [illegible]	[illegible] 37	11 [illegible] [illegible]	[illegible] [illegible]
16	rest 400	rest 400	42 0 07	0 [illegible] 13	[illegible] 10[illegible]	[illegible] 1174	112 17	110 10[illegible]	7[illegible] 61	87 [illegible]	[illegible] [illegible]	[illegible] 34	13.[illegible] [illegible]	[illegible] 7[illegible]
Rest M Range			42 0 34-0 [illegible]	0 41 [illegible]-0 [illegible]	2[illegible]7 184-[illegible]	[illegible] 131 270	11 10[illegible]-11	10[illegible] [illegible]-113	7[illegible] [illegible]	[illegible] 70-10[illegible]	[illegible] [illegible]	[illegible] [illegible]	11 [illegible] 7 07 7 [illegible]	[illegible] [illegible]
Work M Range	3[illegible] 1[illegible]-[illegible]	[illegible] 400-[illegible]	0.21 0 07-0 [illegible]	0 1 10-0 27	137 [illegible]-1[illegible]	1[illegible] [illegible]-100[illegible]	114 107 [illegible]	11 10[illegible]-110	[illegible] [illegible]-10[illegible]	[illegible] [illegible]-10[illegible]	[illegible] [illegible]	37 [illegible]-4[illegible]	[illegible] 13.[illegible]-[illegible]	7[illegible] [illegible]

Symbols and abbreviations according to Pappenheimer et al. Federation Proc [illegible], 1950 Q_{sh} blood flow through unventilated shunt.

(p = **) and not significant, respectively

The *quotient residual volume/total capacity* averaged 29 0 or 110 per cent of that predicted The corresponding value at the first investigation was somewhat higher (31 6 or 120 per cent of predicted value) Only in one case (no 11) was this quotient above what is considered the upper normal range 35 % (20 26)

The *dynamic spirometry* is represented by *maximum breathing capacity* (MBC) *forced expiratory volume in one second* (FEV %) and *maximal midexpiratory flow* (MMF) The observed values are given in table II in absolute terms and in per cent of predicted

ed 126.0 l/min. or 100 per ted value. The corresponding values at the first investigation were 115 7 and 92 The observed increase is however, statistically insignificant. When compared to the non pulmonary group, there is still a probably significant reduction of MBC at the second investigation.

FEV % was found to be somewhat higher at the second investigation in comparison to the first one (97 and 93 per cent of predicted value, respectively) but the difference between the two investigations was not significant. In the non pulmonary group the corresponding value was 101 per cent of predicted, which is not significantly higher than that found at the second investigation.

MMF was found to have increased considerably especially among the females of the group (cases no 11 13 and 14) and

[illegible] (I and II) after "atypical" pneumonia.

		$D_{L_{CO}}$/1 [illegible]				$\dot{Q}_s$ % $\dot{Q}_T$		Oxygen differences mm Hg							
				II			II	$P_{A_{O_2}} \rightarrow P_{c_{O_2}}$		$P_{A_{O_2}} \rightarrow P_{a_{O_2}}$		$P_{A_{O_2}} \rightarrow P_{a_{O_2}}$ breathing air		$P_{A_{O_2}} \rightarrow P_{a_{O_2}}$ breathing O_2	
Obs	% of pred	Obs	% of pred	Obs	% of pred	Obs	% of pred	I	II	I	II	I	II		II
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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$\dot{Q}_T$ total pulmonary blood flow

averaged 3.41 l/sec. or 94 % of predicted value at the second investigation. The corresponding values at the first investigation were 2.57 and 69. The observed difference between the two test occasions was statistically significant (p =) I comparison with the non-pulmonary group, MMF was, however, still significantly lower at the second investigation.

The *nit gen wash-out index* was on an average 7.32, or somewhat lower than that found at the first investigation (8.57). All subjects thus had an index within normal limits, and the average value was in close agreement with that found in the non-pulmonary group.

To *summarize* the lung volumes were found to have increased from the first to the second investigation, the increase in TC being probably significant. In comparison with the non-pulmonary group presented in the first chapter, however they were still somewhat reduced at the last investigation.

The verage values for MBC, FEV % and MMF were found to be higher at the second investigation, but the observed increase was statistically significant only for MMF. In comparison to the non-pulmonary group, MMF was, however, still significantly lower at the second *investigation*.

Al eolar entilation pulmonary diffusing capacity blood-gas tensions and anatomical shunts were studied at rest in supine position and during submaximal exercise in sitting position. The results obtained at the two investigations (I and II) are given in table III.

Table III Ventilation diffusion capacity and related values in 9 subjects at two test

Case no.	Work load kpm/min.		V_D/V_T		V_{O_2} ml/min STPD		$P_{A_{O_2}}$ mm Hg		$P_{a_{O_2}}$ mm Hg		$P_{a_{CO_2}}$ mm Hg		$D_{L_{CO}}$ ml STPD/min/mm Hg	
	I	II	I	II	I	II	I	II	I	II	I	II	I Obs.	II % of pred.
2	rest 600	rest 600	0.30 0.30	0.30 0.16	272 1264	278 [illegible]	105 100	106 110	78 [illegible]	83 90	[illegible] 40	[illegible] 37	9.07 22.40	77 [illegible]
5	rest 400	rest 400	0.[illegible] 0.21	0.31 0.[illegible]	250 1100	271 1046	114 117	102 116	76 [illegible]	78 87	33 25	37 33	18 [illegible]	102 [illegible]
7	rest 100	rest 600	[illegible] 0.17	0.41 0.1	189 1307	190 1278	111 125	107 113	84 [illegible]	83 86	30 [illegible]	34 33	14.61 22.90	84 [illegible]
9	rest 600	400 600	[illegible] 0.11	0.18 0.1	[illegible] 1464	1023 1082	107 100	109 118	82 84	[illegible] 87	34 [illegible]	42 [illegible]	17.[illegible] [illegible] 47	[illegible]
11	rest [illegible]	rest 400	[illegible] 0.[illegible]	0.33 0.[illegible]	184 [illegible]	217 1041	110 116	113 113	[illegible]	79 [illegible]	30 [illegible]	[illegible]	9.[illegible] 13.07	[illegible]
12	300	rest 400	0.[illegible]	0.42 0.27	[illegible]	24 1004	113	101 102	[illegible]	79 [illegible]	[illegible]	[illegible] 42	[illegible]	[illegible]
13	rest 300	rest 400	0.34 0.[illegible]	0.40 0.1	210 [illegible]	131 936	111 107	111 108	[illegible] 84	[illegible] 100	[illegible] 40	[illegible]	7.97 13.[illegible]	[illegible]
14	rest 400	rest 600	0.30 0.[illegible]	0.42 0.14	[illegible] 1083	262 1013	110 114	[illegible] 111	73 103	100 100	[illegible]	[illegible] 37	11.84 [illegible] 07	[illegible]
15	rest 400	rest 400	0.43 0.07	0.30 0.16	234 1033	234 174	112 117	16 100	79 81	97 [illegible]	30 36	30 34	13.[illegible] [illegible]	[illegible] 72
Rest M Range			0.43 .34–0.38	0.41 0.30–0.51	237 184–[illegible]	[illegible] 131 278	103–11	105 [illegible]–113	78 [illegible]	84 78–100	[illegible] 31–[illegible]	30 [illegible]	11.[illegible] 7.97 1 [illegible]	[illegible] 34–[illegible]
Work M Range	380 150–600	480 400–600	0.21 .07–0.30	0.17 0.10–0.27	1137 [illegible]–1463	1301 [illegible]–1083	1 107 125	1 0 102 11	84 64–103	[illegible]	[illegible]	37 33–42	[illegible] 13.63–[illegible]	73 [illegible]

Symbols and abbreviations according to Pappenheimer et al., Federation Proc. 9 602, 1950 Q_{sh} blood flow through anatomical shunt

(p = **) and not significant, respectively

The *quotient residual volume/total capacity* averaged 29 0 or 110 per cent of that predicted. The corresponding value at the first investigation was somewhat higher (31 6 or 120 per cent of predicted value) Only in one case (no. 11) was this quotient above what is considered the upper normal range, 35 % (20 26)

The *dynamic spirometry* is represented by *maximum breathing capacity* (MBC) *forced expiratory volume in one second* (FEV %) and *maximal midexpiratory flow* (MMF) The observed values are given in table II in absolute terms and in per cent of predicted value.

MBC averaged 126.0 1/min. or 100 per cent of predicted value. The corresponding values at the first investigation were 115 7 and 92. The observed increase is, however, *statistically insignificant.* When compared to the non pulmonary" group, there is still a probably significant reduction of MBC at the second investigation.

FEV % was found to be somewhat higher at the second investigation in comparison to the first one (97 and 93 per cent of predicted value, respectively) but the difference between the two investigations was not significant. In the non-pulmonary group the corresponding value was 101 per cent of predicted, which is not significantly higher than that found at the second investigation.

MMF was found to have increased considerably especially among the females of the group (cases no. *11 13 and 14*) *and*

occasions (I and II) after "atypical" pneumonia.

[illegible]		$D_{L_{CO}}$/1 [illegible]				$\dot{Q}_{[illegible]}$ % $\dot{Q}_T$		Oxygen difference mm Hg							
				II			II	$I_{O_2}-P_{A_{O_2}}$		$P_{A_{O_2}}-P_{a_{O_2}}$		$P_{a_{O_2}}-P_{a_{O_2}}$ breathing air		$P_{A_{O_2}}-P_{a_{O_2}}$ breathing O_2	
Obs.	% of pred.	Obs.	% of pred.	Obs.	% of pred.	Obs.	% of pred.	I	II		II	I	II		II
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]		

$\dot{Q}_T$ total pulmonary blood flow

averaged 3.41 1/sec. or 94 % of predicted value at the second investigation. The corresponding values at the first investigation were 2.57 and 69. The observed difference between the two test occasions was statistically significant (p = **). In comparison with the non-pulmonary group MMF was, however, still significantly lower at the second investigation.

The *air gas wash-out index* was on an average 7.32, or somewhat lower than that found at the first investigation (8.57). All subjects thus had an index within normal limits, and the average value was in close agreement with that found in the non-pulmonary group.

To *summarize* the lung volumes were found to have increased from the first to the second investigation, the increase in TC being probably significant. In comparison with the non-pulmonary group presented in the first chapter, however, they were still somewhat reduced at the last investigation.

The average values for MBC, FEV % and MMF were found to be higher at the second investigation but the observed increase was statistically significant only for MMF. In comparison to the non-pulmonary group, MMF was, however, still significantly lower at the second investigation.

Alveolar ventilation pulmonary diffusion capacity blood gas tensions and anatomical shunts were studied at rest in supine position and during submaximal exercise in sitting position. The results obtained at the two investigations (I and II) are given in table III.

With an average work load of 356 kpm/min. (I) and 489 kpm/min. (II) the oxygen consumption *increased to 1 137 ml/min.* STPD (range 649—1 563) and 1 301 ml/min. STPD (range 935—1 803) respectively.

The relation between physiological dead space and tidal volume (V_D/V_T) was, at both investigations, *found to be unchanged* at rest and to *decrease slightly* from 0.21 (I) to 0.17 (II) during exercise. All subjects of the group were, at both occasions, within normal limits and the slight decrease observed during exercise was not statistically significant.

Alveolar ventilation as indicated by $P_{A_{O_2}}$ and P_{CO_2} was within normal limits in all cases of the group at both investigations except in one case (no. 7) whose values at the first investigation indicated slight alveolar hyperventilation. The average value of $P_{A_{O_2}}$ was found to be somewhat lower at the second investigation both at rest and during work. The difference was, however statistically insignificant.

Arterial oxygen tension (P_{O_2}) was found to have increased both at rest and during exercise to within normal limits (15) in most cases at the second investigation. The increase from I to II averaged at rest 8 and during exercise 6 mm Hg. These differences are, however, not statistically significant.

The *anatomical shunt* $\left(\frac{Q_{sh}}{Q_T}\%\right)$ was found to have decreased from an average value of 9.94 % of cardiac output at the first investigation to 7.30 % at the second one. The shunt was reduced in all cases except two (nos. 2 and 5) in which slight increases were observed.

Diffusion capacity of the lungs for carbon monoxide (D_{LCO})

D_{LCO} at rest increased from an average of 11.06 ml/min./mm Hg (range 7.97—17.22) or 59 % of predicted normal value at investigation I to 13.22 ml/min./mm Hg (range 6.33—24.76) or 72 % of predicted value at investigation II, the increase being statistically significant (p = **)

When related to midcapacity (D_{LCO}/l BTPS midcapacity) however, no significant difference in D_L between the two investigations could be observed, the value (in % of predicted) being 68 and 70 respectively.

During exercise D_{LCO} increased from an average of 20.66 ml/min./mm Hg or 73 % of predicted normal value (I) to 26.12 ml/min./mm Hg or 78 % of predicted normal value (II). This increase was statistically not significant. D_{LCO}/midcapacity during exercise was found to be almost unchanged and, when expressed in % of predicted normal value, somewhat lower at the second investigation than at to the first one.

In comparison with the non-pulmonary group, presented in Chapter I, D_{LCO} was significantly low at rest and during exercise as well at the first as the second investigation. D_{LCO}/midcapacity at rest and during exercise was somewhat low at both investigations, the differences between the groups being probably significant (p = *). The individual changes of D_{LCO} and D_{LCO}/MC during exercise in per cent of predicted normal value are shown in fig. 14.

To *summarize* at the second investigation the alveolar ventilation was found to be within normal limits in all cases and to be rather unchanged, when compared to the first investigation.

The arterial oxygen tension was shown to have increased both at rest and during exercise and to be within normal limits.

The anatomical shunt was in most cases more or less reduced but still somewhat larger than normal.

$D_{L_{CO}}$ in absolute terms, was found to have increased both at rest and during work, but was significantly low in comparison to the non-pulmonary group. $D_{L_{CO}}$ in relation to midcapacity was found to be almost unchanged.

Discussion

It has been shown in the present follow up study that the anatomical shunt of moderate size observed at the first investigation was reduced considerably after about six months in most cases studied. In only two cases, however, the shunt was found to be within the normal variation (2, 4) after this time interval. It may be assumed that the observed decrease of the shunt is caused by a corresponding opening up of a number of non-ventilated or collapsed alveoli in the affected parts of the lung parenchyma, while other alveoli will remain non-ventilated. It is, however, impossible to say to what extent these remaining areas of non-ventilated alveoli later on will be opened up and thus be functioning again. Probably some areas of affected alveoli will undergo organization and consequently be permanently non-functioning. In the few subjects studied after a time interval from the end of the acute infectious phase of one year or more, the anatomical shunt was found to be above the normal limit, thus indicating more or less permanent lesions of this type.

Parallel to the observed decrease of the anatomical shunt, the static lung volumes were found to have increased. The total capacity was shown to be normal or almost normal in most cases at the second investigation, the increase being, statistically probably significant. A corresponding increase of the observed pulmonary midcapacity was also found. The increase in lung volume may have been due, at least in part, to the above mentioned process of re-opening of alveoli within the affected parts of the lung parenchyma.

The diffusion capacity for CO at rest and during work was, at the first investigation, low in relation to the predicted normal value, both in absolute terms and in relation to observed pulmonary midcapacity. After about six months a moderate increase of the diffusion capacity in absolute terms was observed at rest and during exercise, but it was still low in relation to predicted normal value in most cases. When related to the pulmonary midcapacity the increase was, however small, apparently due to the fact, that the increase of lung volume (midcapacity) was not parallel to but larger than the increase of diffusion capacity. Thus, even with regard to the observed midcapacity there was a reduction of the diffusion capacity indicating that not only diminished diffusion surface (loss of functioning alveoli) but also changes of thickness and/or permeability of the alveolar capillary membrane may have been involved. In favor of this assumption speaks the fact that the membrane diffusion capacity (D_M) in cases no. 13 and 15 determined at the second investigation, was reduced (see table III, chapter II). Case no. 14 was shown to have a normal membrane diffusion comcapacity and was the only case of the group to show normalized lung function at the second investigation.

The $D_{L_{CO}}$ test was carried out during work sitting, and it was earlier suggested (Chapter I) that, in cases with orthostatic reactions, the displacement of the central blood volume could possibly have been expected to cause a reduction of the diffusion capacity. At the second investigation,

however the orthostatic reactions were found to be rather insignificant and, consequently may not have contributed appreciably to the observed reduction of D_{LCO}

In no case was the anemia of such magnitude that the low value of D_{LCO} could be accounted for by a low hemoglobin concentration

The working capacity was found to be somewhat low in relation to heart volume at the first investigation. The diffusion capacity for CO was also low but the impairment was not of an order to be limiting the oxygen transport capacity as is apparent from the alveolo-capillary oxygen differences These averaged 19 mm Hg at rest and 44 mm Hg during exercise which indicates that there was still a diffusion reserve at the rates of work investigated (19) In some cases however the anatomical shunt may have been of such magnitude as to contribute to the limitation of the oxygen transport. The corresponding oxygen differences at the second *investigation averaged 15 and 40 mm Hg* respectively indicating, that the diffusion reserve, had increased further The increase was however small. Fig 15 shows the relation between D_{LCO} and the corresponding oxygen uptake in the individual cases. All cases of the present series fell above the 70 mm line at both investigations, i.e. they had smaller $P_{A_{O_2}} - \bar{P}_{O_2}$ differences at the rates of work investigated. However in comparison with the subjects of the non pulmonary group they were much closer to this line. The individual changes were varying but on the whole rather small except in cases nos. 9 and 14, with values at the second investigation similar to those observed in the non pulmonary group.

Ventilation seems not to have been a factor limiting the oxygen transport capacity

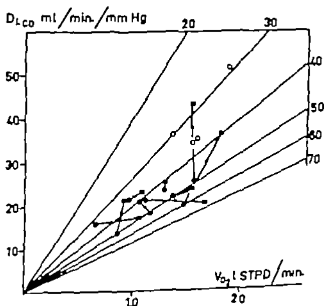


Fig 15 Pulmonary diffusion for carbon monoxide, D_{LCO} ml STPD/min/mm Hg during exercise in relation to the corresponding oxygen uptake (V_{O_2}) ml STPD/min. The straight lines correspond to different values of the $P_{A_{O_2}} - \bar{P}_{O_2}$ differences (see chapter I) Filled circles represent values obtained at the first investigation, filled squares those obtained about six month later Corresponding individual values are connected. (See text.)

at the first investigation. This is indicated by the $P_{I_{O_2}}$ $P_{A_{O_2}}$ oxygen differences, which averaged 39 mm Hg at rest and 35 mm Hg during work, values similar to those earlier observed in normals (19). At the second investigation the corresponding values, 42 and 39 mm Hg, were also within normal limits.

A low stroke volume in sitting position owing to gravitational shifts of the central blood volume could, in some cases at the first investigation, possibly have been a factor limiting the working capacity either alone or in combination with the diffusional disturbances and/or anatomical shunts mentioned. At the second investigation the working capacity was found to be within normal limits in most cases, and the circulatory disturbances due to orthostatic reactions were found to be of rather little importance.

The alveolar-arterial oxygen difference at the first investigation averaged 34 mm Hg at rest and 29 mm Hg during work and, thus, significantly higher than that found in the non-pulmonary group (10 and 13 mm Hg respectively). At the second investigation the corresponding average values were found to be considerably lower at rest 24 mm Hg and during exercise 19 mm Hg. The greater part of the observed decrease may probably have been caused by the decrease of the anatomical shunt discussed above.

Finally it should be stressed, that this follow-up study is to be regarded as an unfinished one, the period of observation being too short to allow any conclusions about the functional conditions of the lungs later in the course following an acute infection of interstitial or atypical pneumonia. To get a definite answer to the question to what extent the observed physiological disturbances will be permanent it would be necessary to continue the present follow-up study for a period of about five years. It is the author's intention to try to realize such a prolonged follow-up study as far as possible as regards the resources available and the possibility to keep in contact with the individual cases of the present material.

Summary

9 subjects, 3 males and 6 females, were investigated in the course following "atypical" pneumonia with a series of cardio-pulmonary function tests at two occasions with an average time interval of 23 weeks. The first investigation was in eight cases carried out a few days or weeks after end of the acute infectious phase when the x-ray picture was almost or entirely normalized and in one cases after 12 months.

The rate of work performed at a pulse rate of 170 beats/min (W_{170}) was found to have increased considerably in relation to heart volume. The heart volume was not significantly different from, although lower than a normal material at the first investigation and in fairly close agreement with this normal material at the second one. Moderate orthostatic pulse reactions were found in some cases at the first investigation, but were almost absent six months later.

The static lung volumes were found to be somewhat low at the first, but within normal limits at the second investigation.

Alveolar ventilation was within normal limits at both investigations.

Nitrogen wash-out index was likewise found to be within normal limits at both investigations, although somewhat higher at the first test occasion in some cases.

The diffusion capacity for carbon monoxide was shown to be somewhat low in relation to predicted normal value at both in-

vestigations at rest and during exercise as well in absolute terms as in relation to mid capacity indicating that the membrane diffusion capacity was more or less affected

The anatomical shunts which were higher than normal in all cases at the first investigation were found to have decreased considerably in all cases but two

Oxygen transport during exercise was at the first investigation in some cases mainly limited by circulatory factors alone or in combination with diffusion disturbances and/or venous admixture due to anatomical shunt. At the second investigation about six months later these factors were hardly of a magnitude as to have a limiting effect on oxygen transport during exercise although, in most cases, still not normalized.

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CHAPTER IV

General Discussion

The purpose of this investigation has been to study the cardio-pulmonary function in the course following the special group of pneumonias, which differ from the classic bacterial or lobar pneumonia pathologically etiologically clinically and radiologically and consequently have been called atypical pneumonias. The term may be adequate in this sense only A more suitable name for these pneumonias would be interstitial pneumonia (pneumonitis) or viral pneumonia when regarded from pathological or etiological point of view (10) Yet, the term atypical" pneumonia has been preferred in this investigation, since it was impossible to ascertain, despite well developed clinical and serological methods, to what extent a patient had suffered from pure interstitial pneumonitis. In general it may be assumed that secondary bacterial invasion of the respiratory tract will occur (6) probably giving rise to more or less pronounced changes, other than interstitial, in the lung parenchyma. In connection with this it may be pointed out that pneumonias, usually referred to as broncho-pneumonias, may be rather ill-defined etiologically and/or clinically Thus, recent investigations (3) seem to show that broncho-pneumonias possibly may be caused at least primary by viruses, thus indicating that lesions of interstitial type are not possible to exclude and that the bounds between these groups of pneumonias are rather undistinctive. However, the present material was selected with the aid of certain criteria (Chapter I) in general applied to in earlier studies on the etiology and clinic of atypical or virus pneumonias (5 10, 12, 13) It must be pointed out that demonstration of specific viruses or other gents, which may induce this type of pneumonias, by isolation, is the only absolutely valid criterion for the clinical diagnosis. Unfortunately this was difficult to carry out at the time for the investigation. However, of possible criteria based on the available laboratory procedures, those referred to in Chapter I, seemed to be most useful in establishing the diagnosis. Applying these criteria, a material with the clinical diagnosis of broncho-pneumonia (1) was found to differ considerably from the present material (Chapter I) Consequently it may be assumed with a certain degree of probability that the pneumonias in the present material were predominantly of viral type.

A control group (the non-pulmonary group, Chapter I) was selected according to criteria presented in Chapter I and investigated in the same way as the atypical pneumonia group. The purpose was to study the possible influence of convalescence *per se* on the cardio-pulmonary function, and if this influence was found to be insignificant,

to make a comparison between the two groups. Unfortunately the anthropometric data of the *non pulmonary* group were found to be somewhat higher than those of the atypical pneumonia group (table II Chapter I) This difference *is explained by* the disparity in the sex distribution within *the two groups* Thus when comparing the observed *absolute* values of different parts of the cardio-pulmonary function the dif*ferences between the groups may have* been overdimensioned. However when comparing the same values related to their corresponding *predicted values this error* will probably be reduced to such a degree as to be neglected

The pathological changes described to be typical in interstitial pneumonitis (4, 7 8, *10 17 19 22) arouse the question whether* they would be resorbed parallel with the disappearance of the clinical symptoms or to the normalization of the radiological changes in the lung parenchyma or remain more or less unchanged *for a longer* period irrespective of symptoms or x ray lesions Of course this qustion can be answered only *indirectly by studying the corresponding* physiological disturbances of the lung function, if not the evolution of the pathological lesions can be followed directly by biopsy At the time when the investiga*tion was planned the possibilty of perform*ing biopsy in suitable cases was discussed, but it was later found to be impracticable as the needle biopsy gave little information about the microscopical structures of the *lung parenchyma and there were too small* indications to perform an open biopsy

Most symptoms of the acute infectious phase (*fever* myalgias, cyanosis dyspnea etc) seem to disappear *more rapidly* than *the pneumonic changes observed* radiologically and patients who have suffered from atypical pneumonia are often discharged before the x ray picture is totally normalized *Symptoms* and signs which seem to remain more or less pronounced after the end of acute phase, are fatigue, cough and *dyspnea on effort The fatigue, which often* may be considerably pronounced for weeks or months will most likely be explained as *a phenomenon* on of convalescense, possibly in combination with orthostatic factors, but is probably not related to the disturbances observed in the lung function except in a few cases with an impairment of the lungfunc*tion of such a degree as to cause anoxia even* at rest. The cough, which in many cases was *found to have a considerable* duration, seems to be unrelated to the degree of impairment of the lung function One case (no. 14) *thus had an almost* normalized lung *function* at the second investigation about six months after the end of the acute stage of pneumonia but was still subject to some cough. One explanation of this symptom, may *perhaps to some extent, be a succesive re*solution of secretion in non ventilated alveoli within the affected parts of the lung parenchyma

The feeling of breathlessness during *physical* work *could in a few cases at the first* investigation *have been related to a* marked impairment of the lung function, limiting the oxygen transport capacity In other cases this subjective feeling may possibly have been caused *by the general* physical weakness and unfamiliarity with physical *effort* after a long period of inactivity

To *summarize* in general there seems to be a *little relationship between the symptoms* and the physiological disturbances in the course following the acute *phase of* pneumonia. Further these symptoms are subject to large variations. Consequently *it is* hardly

possible to draw any definite conclusions concerning the functional state of the lungs from the symptoms present in the course following the acute pneumonia.

The relation between the x-ray findings and the degree of functional impairment also showed large variations. At the first investigation a few days to some weeks after the end of acute phase several cases had no visible parenchymal lesions on x ray although moderate anatomical shunts and more or less pronounced impairment of diffusion were present. At the second investigation most cases were still shown to have significant disturbances of the lung function, though less pronounced, but radiologically normal or almost normal lung parenchyma. Similar conditions have been reported by Holmgren and Svanborg (11) to be present in patients with sarcoidosis. Thus, in a group with hilar lymphnode enlargement but without visible parenchymal lesions on x-rays, disturbances of the diffusion were found, indicating that parenchymal changes may not be excluded. This has also been verified by the fact that parenchymal changes could have been present in lung biopsies from cases with bilateral hilar lymphomas without parenchymal changes on -rays (15).

From the above discussion it may be concluded that the only way to get exact information about the conditions of the lungs in the course following pulmonary infections of this type seems to be investigation of the cardio-pulmonary function with the aid of physiological methods such as those employed in the present study. Repeated investigations are more valuable than single ones for arriving at prognosis of the observed changes. Unfortunately the possibility to carry out such a series of physiological investigations is limited by the rather complicated methodology requiring a well equipped laboratory and by factors of practical nature. (Difficulties to get the subject to co-operate etc.) Such investigations should however be performed in more severe cases.

The further evolution of the physiological disturbances shown to be present up to about six months, and probably more, after the end of acute infection, is difficult to predict from the results obtained in the present investigation. The follow-up study should be continued, if possible, for a considerable period, perhaps as long as five years, in order to secure sufficient data for further conclusions about to what an extent the remaining disturbances of the lungfunction will be permenent. However, it seems reasonable to assume that a certain impairment of the diffusion may be permanent, probably due to changes of the pulmonary membranes within affected parts of the lung parenchyma. A somewhat high anatomical shunt may in certain instances remain for years, as was demonstrated in a few cases investigated one year (case no. 21 Chapter II) or more (cases nos 2, 3 and 4, Chapter I) after the end of acute infection. In others, in contrast, the anatomical shunt was found to be almost normalized after about half a year (cases nos. 13 and 14). The results are, thus in this respect varying, and no definite conclusions can be drawn.

Of interest is the question of the possible relation between the ge of the patients and the evolution of the observed impairment of the lungs. In the present material a considerable individual variation was shown to exist with regard to the degree of impairment of the different lung functions about six months or more after the end of acute pneumonic phase. However in respect to the observed change of the anatomic shunt, it seems reasonable to suppose that normalization will occur more frequently in subjects

below the age of *fifty* (table III, Chapter III) and thus that a certain relation to age may exist. The evolution of the diffusion impairment, on the other side, shows slight relationship to age. Thus, the *diffusion capacity* in absolute terms and in relation to lung volume was shown to remain somewhat *low* after half a year in subjects below the age of fifty However a follow up of these cases during a longer period would be necessary for securing data on which to base *further conclusions.*

Clinically the results obtained in the present investigation, are of interest. In general, the patients have been regarded as convalescents for about 2—4 weeks after discharge and are on sick leave during this period. A control of the x ray and blood picture is usually made after this time and if these are shown to be normalized, the subject is allowed to start working even if more or less pronounced symptoms or signs (cough, fatigue etc.) still remain. The *present investigation has shown that a certain* impairment of the lung function may persist for probably more than half a year after the acute pneumonic phase. *Consequently* if the subject, after the period of convalescence, *still complains about certain symptoms from* the lungs a physiological investigation of the lung function should be made even if the x ray is normalized at this time.

When anatomical shunts of considerable size alone or together with other disturbances of the lungfunction are shown, physiotherapy of the thorax might possibly be a valuable complement to the current treatment. *Probably* an even more positive effect of the such therapy would be obtained, if this was started already in the acute stage of the pneumonia. The usefulness of this form of therapy prophylactically against post-operative atelectasis in the lungs (16, 20, 21) or in *the paralytic stage* of poliomyelitis (14) is well known. An early initiation of physical treatment in atypical" *pneumonias* (and possibly pneumonias in general) would thus probably counteract further development of atelectatic areas within the affected parts of the lungs and possibly *contribute to a more rapid normalization* of the observed anatomical shunts in the course following the acute phase.

Finally something will be said about the possible relation between virus pneumonias and other clinically defined lung diseases with fibrosis. Thus among the possible etiologic factors of the Hamman-Rich syndrome (acute interstitial fibrosis) virus or interstitial pneumonia has been mentioned (9 18) *However this is only an assumption*, as no real evidence in this respect has been presented up to now The results of the present investigation are not contributing to an answer to this question. But, as already pointed out, the period of observation is relatively short and a continued *follow up study of the material would possibly give* more valuable information in this respect.

The possibility of an increased sensibility *to infections of the respiratory airways after* an atypical pneumonia passed through, must be taken into consideration. Repeated pneumonias would *presumably* result. *With* each new pneumonia, the impairment of the lung function would be expected to increase *progressively parallel to the* patho-anatomical lesions of the affected parts of the lung parenchyma. The *final* result would *probably* be a *fully developed fibrosis. However* it must be pointed out that this development is outlined on the basis of assumptions and that only by means of a follow-up *study of long duration* can this question be thoroughly elucidated.

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The possibility of an increased sensibility to infections of the respiratory airways after an atypical pneumonia passed through, must be taken into consideration. Repeated pneumonias would presumably result. With each new pneumonia, the impairment of the lung function would be expected to increase progressively parallel to the patho-anatomical lesions of the affected parts of the lung parenchyma. The final result would probably be a fully developed fibrosis. However it must be pointed out that this development is outlined on the basis of assumptions and that only by means of a follow-up study of long duration can this question be thoroughly elucidated.

The *capillary blood volume* was found to vary considerably being either normal or reduced.

It was concluded that the observed decrease of D_M might have been caused not only by a decrease of the functioning diffusion surface but also by changes of the pulmonary membrane itself

In *Chapter III* the results of follow-up study of the cardio-pulmonary function in 9 cases from the "atypical" pneumonia group are presented. The first investigation was in most cases carried out a few weeks after the end of the acute phase of pneumonia, and the interval between the two investigations averaged about six months.

The somewhat low working capacity observed at the first investigation was found to be almost normalized at the second one. The influence of posture during work was much less pronounced at the second than at the first investigation.

Ventilation and *distribution* were within normal limits in all cases at both investigations.

The *diffusion capacity* in absolute terms and in relation to midcapacity was somewhat low at the first investigation. Six months later significant increase of D_{LCO} was shown, but when related to midcapacity it was almost unchanged, indicating that the membrane diffusion component may have been more or less affected after this time interval

The *anatomical shunts* which were higher than normal in all cases at the first investigation, were found to have decreased considerably in all but two cases six months later.

Oxygen transport during exercise was, at the first investigation limited by circulatory factors alone or in combination with diffusional disturbances and/or venous admixture due to anatomical shunts. At the second investigation these factors were hardly of such a magnitude as to limit the oxygen transport capacity during exercise although, in most cases, they were still not normalized.

From the results of the present study it seems possible to draw the following conclusions

1. Subjects who have suffered from atypical pneumonia (acute interstitial pneumonitis) may be expected to have a varying degree of impairment of the cardio-pulmonary function for at least six months after the end of the acute stage of illness.

2. There seems to be little relationship between the degree of impairment and the signs or symptoms in the post infectious phase, except in a few cases with pulmonary impairment of such a degree as to limit the oxygen transport capacity during *physical strain*.

3. The degree of functional disturbance seems to be unrelated to the x-ray picture in the post-infectious phase. This is shown by the fact that various functional disturbances may be observed even in subjects without visible lesions on x-ray

4. A certain, progressive improvement of the cardio-pulmonary function may be expected during the first months after the acute stage of pneumonia, but some degree of impairment will probably remain even after six months or more, irrespective of age.

CHAPTER V

General Summary and Conclusions

The cardio-pulmonary function was studied in 21 subjects at various times in the course following atypical pneumonia, and in 12 subjects convalescents after acute infections and with no demonstrable involvement of the lungs. In the atypical pneumonia group most subjects had suffered from primary atypical pneumonia with lesions of the lung parenchyma, probably of interstitial type. The x ray picture was at the time of the investigation, almost or entirely normalized.

In *Chapter I* the results of the first investigation, in most cases performed some weeks after the end of the acute infection, were presented. The cardio-pulmonary function in the non pulmonary group was found to be in close agreement with earlier normal series. In the atypical pneumonia group the heart volume and physical working capacity were shown to be somewhat lower than in the non pulmonary group. Orthostatic reactions both at rest in standing and during work in sitting were a little more pronounced than in the non pulmonary group.

Alveolar ventilation was normal or almost normal in all cases but one who showed signs of hypoventilation. The cause of this was obscure.

The *diffusion capacity* of the lungs was reduced at rest and during exercise both in absolute terms and in relation to BSA and midcapacity.

Anatomical shunts ranging from 6 to 15 % of cardiac output were found, suggesting that small areas of non ventilated alveoli remain in the affected parts of the lungs even after normalization of the x-ray picture.

The lung function was not impaired to such a degree as to be a limiting factor of the oxygen transport except in some cases with significantly increased alveolo-capillary oxygen differences during work, indicating that impairment of diffusion alone might be a limiting factor. Otherwise, oxygen transport seemed to be limited to the greatest extent by circulatory factors either alone or in combination with diffusion disturbances and/or venous admixture.

In *Chapter II* the pulmonary membrane diffusion capacity (D_M) and pulmonary capillary blood volume (V_C) were studied at various times in the course following the acute phase of atypical pneumonia. The clinical diagnosis was in most cases primary atypical pneumonia. One case had suffered from psittacosis. The x ray picture was at the time of investigation, in most cases almost or entirely normalized.

The *membrane diffusion capacity* was shown to be reduced both in absolute terms and in relation to midcapacity of the lungs.

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Stockholm, april 1962

Hans Berven

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CONTENTS

INTRODUCTION

Since the earliest days of arterial blood pressure registration attempts have been made to define the "normal" blood pressure. In the estimation of what should be regarded as the normal range of variation f the arterial blood pressure mainly two methods have been used, namely the range found in defined part f representative sample of the population (Rubenk et al. 1946, Gover 1948, Master et al. 1950, Hamilton et al. 1954, and thers) and, secondly th upper limit fo the arterial blood pressure has been set at the level of the blood pressure beyond which there is an over mortality (Fisher 1914 Symonds 1923 Robinson & Brucer 1939 and others)

The first method is based on the conception of normalty for population with reference to the frequency distribution of the blood pressure in the population. The limits of the normal blood pressure can be given with different measures of dispersion around the arithmetic mean (M) All such limits are arbitrary The normal range of variation is usually given as $M \pm 2s$ which implies that about 95 per cent of the observations fall within the limits.

Classification of series according t sex and age gives a frequency distribution for each class with different means and ranges of variation. The mean value found for each class with its standard deviation gives a more accurat limitation of what should be regarded as normal. The distribution curves f the low age classes are normal. As age increases the curves become kewed, *i.e.* they move to the right and the dispersions increase (Wetherby 1932/33 Britten & Thompson 1923 Hamilton t al. 1954, Boe et al. 1956 Pickering 1960) Holmgren (1955) whose series consisted f 4,864 patients from pri vate practice, found that the distribution curve of the systolic blood pressure in both males and females was skewed t the right. Miall & Oldham (1955) Pickering (1960), and others have stated that the distribution curv was continuous, while Platt (1960) con cluded "that the evidence of tw (or more) distinct populations" was very trong indeed

A given series may also be divided according to other factors, probably related to the arterial blood p essure, *e.g.* body height and body weight. This might offer further possibilities of predicting the normal blood pressure in statistical sense.

Brunton (1909) found th upper limit f the normal range f the blood pressure to increase with ge On the basis of his studies he claimed that the normal blood pressure in young men was 120 mm. Hg with an increase to 150 mm. Hg in the higher age groups. Of other authors who have studied the blood pressure in large series, mention might be made of Rubenk et al. (1946) Gover (1948) Master t al. (1950), Hamilton t al. (1954) and Boe et al. (1956) The results btained by these authors sh w certain discrepancies which can often, of course, be ascribed, in part, to differences in the series compared e.g in respect of sampling, but at the same

time the differences suggest that *inter alia* environmental factors and race should also be considered The underlying causal biological factors are of only subordinate importance in the present investigation The essential thing is that attention has been drawn to factors enabling further precision of the prediction of the normal blood pressure from a statistical point of view

The second method for determining the normal blood pressure is based on a biological medical concept of normality with reference to the relationship between the level of the blood pressure and the general mortality It is above all, *life insurance companies that have* made such investigations According to this *method the limit for the normal* blood pressure is defined as blood pressure not associated with any over mortality With these approaches individuals are regarded from a statistical point of view as "good" or "bad" risks *i.e regardless of any pathologic condi*tions they might have The mortality in these two groups was studied independent of any biological causal relationship between the blood pressure *and the mortality claimed by different* diseases Using this procedure FISHER (1914) presented a *life insurance material* consisting of 19,330 accepted risks A blood pressure of 150 mm Hg gave a definitely higher mortality rate than the average SYMONDS (1923) reported accepted risks (150 419 men and 11 937 women) at standard rates by the Mutual Life Insurance Company of New York for the years 1907 to 1919 For all males *he found an over mortality at a systolic* blood pressure above 145 mm For those below 30 years in his series he noted that even a blood pressure of more than 140 mm Hg was attended by over mortality A diastolic blood pressure of more than 94 mm for males was regarded by him as possibly *being in the* danger zone

MASTER et al (1943) however pointed *out that the level of the normal blood* pressure in the above-mentioned latter conception of *normality should be* raised for persons above 40 years of age. In a longitudinal investigation of 1,038 patients followed for 4—11 years BECHGAARD (1946) found that the over mortality among persons with hypertension decreased with advancing age.

It is however *a priori* probable that the normal variation of the blood pressure as determined by the two above mentioned methods will not coincide because semantically they represent different conceptions of normality

The purpose of the present investigation was to widen our knowledge of the *qualitative statistical correlations* between the blood pressure and different individual characteristics such as—in addition to age and sex—certain anthroposomatological dimensions and blood lipids In investigations of the plasma *lipids in association with the arterial* blood pressure the authors usually aimed at assessing the significance of these two *factors* in the causation of atheromatous vessel changes. Some in*vestigators have found* correlations between these two factors In view hereof it was decided to study also the plasma lipids for any correlation with the arterial blood pressure The investigation comprised not only the determinations in the fasting state but also changes in these lipids after fat ingestion *in the* belief that any changes between different *individuals regarding the plasma* lipid pattern might be accentuated after fat ingestion

It was also hoped that analyses of the quantitative statistical correlations between blood pressure and the characteristics studied would enable an increased precision of the *prediction of the normal* limits of the blood pressure

MATERIAL

Attempts were mad to collect relatively representative part f the population that were in average good health and able to work. It was not intended to secure a series of persons in flawless health, but t the same time it was not intended to include persons with physical defects r with diseases that might influence the fat metabolism.

The material consisted of 85 males and 107 females aged 11 to 69 years. The series is distributed among 10 year classes in Table 1 Unless therwise stated, the statistical calculations are based on this distribution In th 10–19 year age class the males were relatively evenly distributed, while all of the females were 16 years or abo e. (The age distribution f the entire series is given in Appendix I) Of the males, ne was aged 11 whose voice had not broken. Menstruation had started in all th females and all stated that they had not been pregnant during the last 12 mo ths N attempts were made t mak the measurements on any particular day of the menstrual cycle. N distinction was made between post menopausal and the remaining females.

Table 1 *Age distribution of males and females in the present material*

Group age	Number of subjects	
	males	females
10–19	12	22
20–29	12	22
30–39	13	19
40–49	16	15
50–59	15	13
60–69	17	14
Total	85	107

The material included various categories of males and females such as hospital personnel (e.g doctors, medical students, mechanics, janitors, nurses nurse students, chars men) firemen, policemen, insurance agents, school children and house-wives.

The in estigation was carried out t the Department of Medicine, Lund, during the period 4.3 1955–20 12.1957 All the individuals were examined by the autho personally The examinations were carried out during different seasons At the time of the examination 181 of the persons included in the present investigation were living and working in Lund and 11 in the vicinity of Lund, Sweden

As mentioned above, the persons included in the present investigation felt healthy and were in full-time employment Of the original material, persons wh reported that they had had attacks f biliary colic and those wh had been subjected t gastric resection f example, were excl ded

The present material included persons with the following known pathological conditions 1 man with irritable colon, 3 men who had had attacks of renal colic, 1 w man who had been perated upon f cancer of the breast 8 years previou ly and who now showed no clinical evidence of metastasis, 1 man with clinically healed (euthyroid) ex ophthalmic goitre afte subtotal strum-

ectomy 16 years previously 1 man who had for 8 years auricular fibrillation of unknown origin

In none of the patients accepted could any xanthomatous changes be detected on careful examination of the skin When questioned all the patients denied having heart symptoms in the form of breathlessness and palpation on exertion or stenocardia None of the patients showed evidence of active thyreotoxicosis or hypothyreosis Cholecystography was not done

On examination all of the subjects were found to be in a good nutritional state which in view of the social standard of the probands was only to be expected In this connection it might perhaps be mentioned that according to the *official statistics (Statens Jordbruksnämnd* 1958) during the years 1955 1956 and 1957 about 38 37 and 38 per cent, respectively of the dietary calories were covered by fat During those years the *Swedish diet per person per day* contained, on the average, 3 133 3 099 and 3 051 calories and consisted of 128.4 123 6 and 125 0 gm of fat respectively

In the investigation of biological problems use may be made of very large series of individuals, and then the random error will have but little effect on the results But the use of very large groups makes it practically impossible to study many variables, besides which evaluation of the variables studied may also be less uniform If small series are used, the effect of the random error will be relatively greater but it will allow a uniform evaluation of the different *variables and detailed experimental* studies on each individual The present investigation aimed at a detailed registration of body build and the demonstration of changes, if any in the plasma lipids before and after fat ingestion so that it was necessary for practical reasons to limit the size of the material.

VARIABLES STUDIED AND METHODS OF REGISTRATION

In the study described below the systolic and diastolic blood pressures were studied for any correlation with age, sex, and different anthroposomatological dimensions as well as the plasma lipids in the fasting state and after fat ingestion.

ARTERIAL BLOOD PRESSURE

The arterial blood pressure can be measured by direct and by indirect methods. The direct method, e.g. with a cannula or catheter in the artery presumably records the actual pressure in that segment of the vessel studied during the cardiac cycle. The indirect method in which the blood flow is occluded by the cuff and the pressure then recorded during gradual relief of the compression is attended by certain sources of error which may influence the results.

Good agreement has been found between the results obtained by the direct method and the indirect method. As to the systolic blood pressure, it has been found that the indirect method gives values regularly 3–4 mm. Hg below those obtained by the direct method (HAMILTON et al. 1936). BORDLEY et al. (1951) gave a corresponding difference of 3–4 mm. Hg with a variation of ± 8 mm. Hg.

Agreement between the indirect and direct measurement of the diastolic blood pressure is dependent on the use of the blood pressure level noted—by the indirect method—when the Korotkow sound abruptly begins to diminish or the value when the sound has just disappeared. In the former case the value recorded will be 5–10 mm. higher than in the latter. The diastolic blood pressure, as measured by the direct method, is usually much lower than the value noted on abrupt diminution of the sound by on the average, 9 mm. Hg (HAMILTON et al 1936 STEELE 1941/42) 8 mm Hg (BORDLEY et al. 19 1) and slightly lower than the value noted on disappearance of the sound, 1 mm. Hg (STEELE 1941/42). Occasionally such as in persons with a large circulatory minute volume or in patients with a high pulse pressure, however the blood pressure recorded on disappearance of the sound is much lower than the diastolic blood pressure noted by the direct method (KOTTE et al. 1944 BERGEN et al. 1954).

The indirect method with occlusion of the blood flow thus appears to reflect the intra-arterial pressure variations satisfactorily during the cardiac cycle. For practical reasons it was therefore decided to choose the occlusion method in the present investigation.

The technique used for the measurement of the arterial blood pressure with the cuff method was largely in accordance with the recommendations given by STRÖM & WERKÖ (1958) at the request

* standardized methods and symbols, see Appendix 3

ectomy 16 years previously 1 man who had for 8 years auricular fibrillation of unknown origin

In none of the patients accepted could any xanthomatous changes be detected on careful examination of the skin When questioned all the patients denied having heart symptoms in the form of breathlessness and palpation on exertion or stenocardia None of the patients showed evidence of active thyreotoxicosis or hypothyreosis Cholecystography was not done

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3 Side of the lateral part of the thorax over the lower ribs midway between the axilla and th iliac crest.
4 Abdomen to the right of the umbilicus.
5 Arm halfway between the houlder and elbow over the triceps muscle
6 Thigh halfway down over the rectus femoris muscle

The skinfold measurements were mad in a room with a temperature of 0—22°C. The caliper was pplied at 1 cm. from the fingers by which the skin was lifted so that proper fold (a complete double layer) w s formed. Th values for the subcutaneous fat were given as the thickness of the skinfold in millimetres, which means twice the thickness of th cutis + subcutis. Three estima tions were made from each site and the a erage skinfold thickness in millimetres was taken s the representative value for further calculations.

The muscle factors were determined in accordance with the directions of STOLTZ & STOLTZ (1951) and LINDEGÅRD (1953 1956) The correlation between the gross muscular trength and its morphological correlation, i.e. muscle mass, w tudied by LINDEGÅRD and he found in series of 20-year old army men that the gross muscular trength in statistical correlation studies might be accepted a the measure f the amount of muscular tissue of the body (LINDE GÅRD 1956)

The gross m scular trength of the right well the left handgrip, the shoulder pull and the houlder thrust was recorded. Three recordings were taken for each muscle-group, the highest alue was taken as representati f the muscularity of the muscles under con ideration The dynamometers were calibrated immediately bef re the beginning of the investigation and they were checked on various occasions during the investigation.

Investigation of skeletal factors in cluded stature, radial length, tibial length and femoral condylar breadth The radial and tibial length represented the length factor and femoral condylar breadth the sturdiness factor (LINDE GÅRD s reference system)

The stature was measured to the nearest centimetre with the subjects erect barefooted, and with the head in such a position that the Frankfurter plane i.e the imaginary line between Orbitale and Tragion, was horizontal.

The radial length was measured in accordance with MARTIN (1928) The Radiale is the most proximal point of the radial capitulum in the radio-humeral articular groove. The Stylion radiale is the summit of the radial tyloid process The linear distance in millimetres between these two reference points was taken as the length of the radius

The tibial length was given in accord ance with MARTIN (1928) as the linear distance in millimetres between the Tibiale and Sphyrion. The point Tibiale is the medial margin bordering on the articular groove between the tibial and femoral bones Point Sphyrion is the distal point of the medial malleolus.

The femoral condylar breadth wa taken as measure of the sturdiness factor and the measuring technique described by LINDEGÅRD was pplied. The linear distance in millimetres between the medial and lateral surface of the right condyle was determined with the calipers lightly pressed against the condyle

PLASMA LIPIDS

The proband were tudied with respect to the plasma lipids in the fasting tat and after f t ingestion.

Th total lipids were determined by the method described by SWAHN (195., 1953) with slight modifications. The

of *Svensk förening för cardiologi* and those given by American Heart Association and the Cardiac Society of Great Britain and Ireland together (1939) The blood pressure equipment, which was a Mercury Erka manometer was calibrated on various occasions during the investigation and was found to give accurate values The blood pressure was measured with the subjects lying after about 10 minutes rest The cuff which was 12 cm in width, was placed on the arm with the lower edge 2—3 cm above the antecubital space The stethoscope was placed over the brachial artery in the antecubital space and the cuff was rapidly inflated. It was then deflated at a rate of roughly 2 to 3 mm per second and the value noted when the Korotkow-sound just began to be audible was noted as the systolic blood pressure The value noted when the Korotkow sound disappeared was taken as a measure of the diastolic blood pressure because, in view of what was said above, this value agrees best with the intra arterial diastolic blood pressure measured. The examination was performed between 10 a.m and 6 p m. The blood pressure was read to the nearest 5 mm Hg

In some investigations the authors tend to round off the blood pressure recordings to the nearest 10 mm Hg (JANEWAY 1913 FABER 1924) In other investigations this tendency is more pronounced for the diastolic than for the systolic reading (MASTER et al 1950) The present data were therefore checked for any such registration bias, which concerning the diastolic blood pressure would have been of great importance, and it was found that the last digit of the systolic blood pressure for males was 0 in 42 cases and 5 in 43 and for the women the corresponding values were 54 and 53 respectively The corresponding results for the diastolic blood pressure were 48 and 37 for the males and 53 and 54 respectively for the females

ANTHROPOSOMATOLOGICAL DIMENSIONS

Variations in human body build can be studied by measurement according to different reference systems Of the methods available for the present investigation (cf SCHWIDETSKY ROESING 1959 REES 1960) the reference system described by LINDEGÅRD appears to be most suitable LINDEGÅRD s (1953 1956) system implies a purely objective registration of the general body build on the basis of the following four variables length, sturdiness, muscle and fat factors These variables reflect the amount and distribution of the quantitatively dominating tissues of the body

The anthroposomatological dimensions studied in the present investigation were those which, according to LINDEGÅRD represent the above-mentioned 4 dimensions Unless otherwise stated, all measurements were made on the right half of the body Body height was taken as a skeletal dimension.

The body weight was measured to the nearest 0 1 kg The males were weighed naked and the females with drawers on

The fat factors were studied by measurements of skinfold thickness with a replica of the calipers especially constructed for this purpose by KEYS (cf KEYS & BROZEK 1953) The pressure applied by the caliper was 10 gm /mm [2] and the area of the contact surface was 20 mm.[2] Skinfold measurements were taken at six different sites of the body in accordance with the technique devised by SKERLJ et al. (1953) and applied by LINDEGÅRD (1956) in a Swedish series

1 Chin under the mandible, with the peak of skinfold extending from chin to neck in the midline
2 Back just below the angulus scapula.

hours after f t ingestion (162 double determinations) ± 3.3 per cent f the chylomicrons, ± 3.6 for the β-lipoproteins and ± 2.5 for the -lipoproteins.

Ingestion of fat. The probands were instructed not to eat any fat after 6 p.m. and no food at all after 9 p.m. the evening before the test. At 7 15 a.m. on the day of the examination a blood sample was collected by venipuncture before the subject had received anything to eat, and after a test meal, which consisted of 100 gm. of unsweetened pple-sauce, 500 ml. of milk cream (1.—14 % fat), 100 ml. of coffee, 2 lumps f sugar 20 gm. of butter and 20 gm. of hard bread. Blood samples were collected by venipuncture 2, 3, 4 7 and 9½ hours after the meal. The subjects were instructed not to eat, drink or smoke during the experiment until after the 7 hour blood sample had been collected The subjects were then given 100 ml. of coffee with 2 lumps of sugar During the day of the experiment the probands were carrying on with their usual work.

modifications consisted largely in the use of EDTA Na_2-plasma instead of serum dissolution of triolein in butanol, and in an increase of the amount of plasma and triolein solution, respectively from 0.02 ml to 0.10 ml.

The reason why EDTA Na_2-plasma was chosen instead of serum was that a number of other examinations were performed at the same time as those accounted for here and for which among other things a relatively large amount of blood was necessary. By using plasma instead of serum the necessary amount of blood could be decreased. In addition plasma could be obtained 3—4 minutes after sampling which was also of importance for related investigations. The purpose of the increase in the amount of plasma and triolein respectively in the samples was to decrease the error of the method.

SWAHN's method was studied in thorough detail, but since the results obtained were substantially in agreement with those reported by SWAHN (1952, 1953) it was not considered necessary to give a detailed presentation of this methodological study (THUEDSSON 1962). The use of EDTA Na_2 plasma instead of serum had no demonstrable effect on the results. It was thus found that EDTA Na_2-plasma and serum from the same blood gave values for the total lipids, which did not differ significantly from one another in samples collected during the fasting state or in samples obtained 3 hours after fat ingestion.

According to DAHLBERG (1948) the error of a method can be calculated by formulae: standard error of a difference $= \pm\sqrt{\frac{\Sigma d^2}{N}}$ and the standard error of a single determination $= \pm\sqrt{\frac{\Sigma d^2}{2N}}$ where d is the difference in double determination and N the number of double determinations. The standard error of a single determination of total lipids in fasting plasma (138 double determinations) was ± 4.2 per cent and in plasma 3 hours after fat ingestion (140 double determinations) ± 4.5 per cent.

The lipoproteins in the plasma were determined after electrophoretical separation on filterpaper using the apparatus and the buffer described by LAURELL et al. (1956). After colouring with Sudan Black according to the method of SWAHN (1952, 1953) the "electrophoretic paper" was cut with the coloured start fraction in one piece, the α-lipoproteins in another and the β-lipoproteins in the third so that each fraction could be eluated by itself. Since the lipoproteins with high molecular weight are absorbed by the filter paper (SWAHN 1953) the start fraction contained also lipoproteins other than chylomicrons. This fraction was nevertheless designated "chylomicrons" in the present study.

The method for determining lipoproteins was also made the subject of a thorough methodological study. The results obtained did not differ substantially from those described by SWAHN (1952, 1953) so that it was not considered necessary to burden the present article with a detailed description of the methodological studies (THUEDSSON 1962). The use of EDTA Na_2 plasma instead of serum was not found to have any effect on the results. Thus no difference was obtained between the results of simultaneous electrophoretical determinations of EDTA Na_2 plasma and serum from persons in the fasting state or from persons 3 hours after fat ingestion.

The standard error of a single determination for fasting value (175 double determinations) was found to be ± 2.8 per cent for the chylomicrons, ± 3.0 for the β-lipoproteins and ± 2.3 for the α-lipoproteins and for the values 3

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QUALITATIVE STATISTICAL CORRELATIONS OF THE ARTERIAL BLOOD PRESSURE WITH AGE, SEX, BODY BUILD FACTORS AND PLASMA LIPIDS IN FASTING STATE AND AFTER FAT INGESTION

VARIATION OF ARTERIAL BLOOD PRESSURE WITH AGE AND SEX

AGE

BRUNTON (1909) found the systolic blood pressure in older people to be higher than in younger An increase of the average systolic blood pressure from 120 mm at the age of 20 up to 135 mm at the age of 60 years was found by ROGERS & HUNTER (1919) in a life insurance material of 150 000 deter minations In a Danish series which consisted of 171 apparently healthy males and females aged 21 to 60 years, FABER (1925) found an increase of the systolic blood pressure with age

An increase of both the systolic blood pressure and the dia tolic blood pressure with age was demonstrated by SYMONDS (1923) GOVER (1948) and HAMILTON et al (1954) Similar results have been reported by WETHERBY (1932/33) whose series con isted of 2,282 men and 3,258 women admitted to the out patient department of the University of Minn esota Hospital and by BOE et al (1956) whose material comprised 67 976 persons from Bergen

In a series consisting of 8 645 army officers found to be healthy on physical examination DUNHAM (1925) found a significant correlation between the systolic and the diastolic blood pressure respectively and age and no influence of body weight on the correlation could be demonstrated

In 3 426 men, aged 40 to 95 years, RUSSEK et al. (1946) found an increase of the normal systolic blood pressure with age, while the normal diastolic blood pressure tended to decrease after 50 years In a series of 2 998 men and 2,759 women, aged 65—106 years, MASTER & LASSER (1961) found that in males, after the age of 65 the blood pressure fails to change significantly with advancing age In females, however they found that the blood pressure continued to rise somewhat after 65 and to reach a maximum at 70—74 years and then to decline

ALVAREZ & STANLEY (1930) however were unable to find any appreciable va riation in the systolic or diastolic blood pressure with age in their series consi sting of 6,225 prisoners ROBINSON & BRUCER (1939) found in life insurance material, consisting of 7 478 men and 3 405 women that the upper limit for the normal" blood pressure was 120/80 mm Hg and that it did not increase with age HOLMGREN (1955) found among 4,864 patients from private practice in Stockholm that the mode for the systolic blood pressure in both sexes was 125—150 mm Hg up to the age of 60 years, even though the number of patient with systolic blood pressure above 150 mm successively increased.

The curve for the number of out

patients with hypertension showed a gradual and progressive rise up to the age period of 45 years and thereafter an abrupt ascent (Ritsman & Weiss 1930) but after the ge of 70, the incidence drops sharply. Master et al. (1943) found that the number of individuals with arterial hypertension ncreased up to 80 years f age, while the increase of diastolic blood pressure declined after 60 years of age, and tended to fall after the age of 80 years An increase of the frequency f arterial hypertension with dvancing years has also been shown by Britten & Thompson (1924) and Miller (1941)

Investigations on record thus largely how that the verage blood pressure based on the conception of a rmality f a population increases with age in males up to the age of 65 years, and in females up to 0 years. In those investigations in which the blood pressure was evaluated on the basis of a biological medical concept f n rmality it has been claimed that the "normal" blood pressure does not increase with age But this approa h gi es no information as t how the blood pressure increases numerically with age

SEX

M ny thors have tressed that in the lower age classes males ha higher blood pressure than females, but the other way round in the higher ge classes. Symonds (1923) thus found that up t the age f 40 years both the sy tolic blood pressure and the diastolic blood pressure were higher in males than in females afte which the relationship was the rev rse Similar con lusions were arrived t by Holmgren (1955) who found the in ersion point t be 30 years f age Master et L (1950) found the in ersion point f the t lic blood pressure t be t 45 years while the a erage diastolic blood pressure up to 50 years of age wa higher for males than females, after which no difference could be hown.

Faber (1925) found that females in all age classes (21—60 years) invariably had a higher systolic blood pressure than males. In Wetherby's material (1932/33) the women above 39 years had a higher blood pressure than the men and in Gover material (1948) after 35 years f ge

The foregoing data show that, broadly speaking, in the low age classes males have higher blood pressure and *vice versa* in the higher age classes. The inversion point is largely at 40—45 years.

RESULTS AND COMMENTS

On visual inspection the frequency distribution f the systolic and diastolic blood pressure ppeared to be fairly normal f r both males and females The skewness of the two distributions was also studied by calculating the differences between the respective mean and median and the distances of th two quartiles from the median. This revealed that th distribution of the diastolic blood pressure in the males tended t be slightly kewed t the left, whil the othe distributions were normal.

The correlation between systolic and diastolic blood pressure was ignificant f both males ($r = +0.69$) and females ($r = +0.69$) After elimina tion f the influence of age on the co-variation, the correlation coefficients were numerically lower but till signif icant (males $r = +0.56$ females $r = +0.63$)

Both the ystolic blood pressure and the diastolic blood pressure in the males ($r = +0.48$ and $+0.6$) as well as in the females ($r = +0.49$ and $+0.38$) were significantly correlated with age. The scatter diagrams and the regression lines of blood pressure on age for males and f males are gi en in Figs 1—4 The empirical regres ion lines formed by the

arithmetic mean in the different age classes closely followed the respective theoretical regression lines The scatter diagrams showed that the plottings were crowded fairly closely around the respective regression lines

As to the correlation between the diastolic blood pressure and age for males, the values in the 10—19 year class appeared to have a relatively strong influence on the correlation coefficient. It was therefore decided to calculate the correlation coefficient of the relation between the diastolic blood pressure and age in males in the 20—69 year age classes only but no substantial difference in the correlation coefficient was obtained (r = + 0.56*)

The regression lines for systolic blood pressure on age for males and females showed roughly the same slope, and the corresponding correlation coefficients

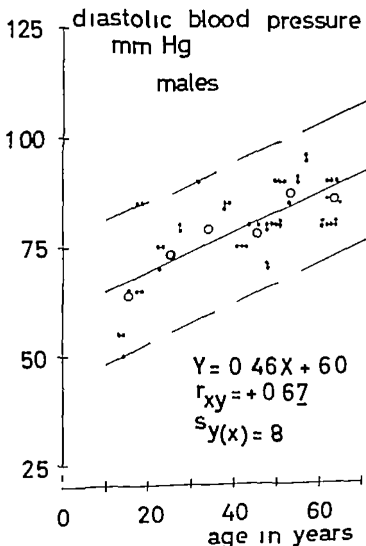


Fig 3 *Scatter diagram of correlation between diastolic blood pressure (Y) and age (X) in males. The continuous line denotes the theoretic regression line of the diastolic blood pressure on age. Th interrupted lines denote the distance of twice standard deviation from the regression line. The circles indicate th arithmetic mean f th diastolic blood pressure in consecutive ge classes.*

were not significantly different ($t = 0.2$). The regression line of the diastolic blood pressure on age was steeper for males than for females, and the two regression coefficients differed significantly from one another ($t_s = 2.8$). The slope of the regression line for males appeared to be fairly strongly influenced by the values in the 10—19 year class. The regression lines were therefore calculated for the diastolic blood pressure in males and females on age for only the 20—69 year age classes, and these regression lines appeared to have the same slope. The corresponding regression coefficients were not found to differ significantly from one another ($t_s = 0.9$).

This finding that the blood pressure increases with age is in agreement with the results in most previous investigations (BRUNTON 1909, SYMONDS 1923, DUNHAM 1927, GOVER 1948, HAMILTON et al. 1954, BOE et al. 1956, and others). The results of the present investigation and those reported by ROBINSON & BRUCER (1939) are not comparable and therefore need not imply a contradiction. The influence of various environmental factors on the blood pressure may be a plausible explanation

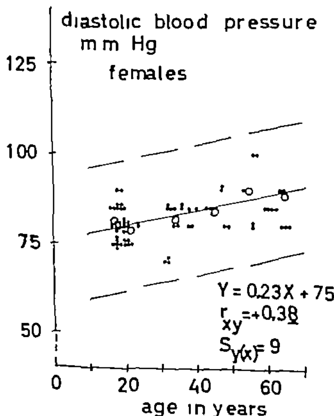


Fig. 4. Scatter diagram of correlation between diastolic blood pressure (Y) and age (X) in females. The continuous line denotes the theoretic regression line of the diastolic blood pressure on age. The interrupted lines denote the distance of twice standard deviation from the regression line. The circles indicate the arithmetic mean of the diastolic blood pressure in consecutive age classes.

for the wide difference between the results obtained in the present investigation and those reported by ALVAREZ & STANLEY (1930) It should be observed that the average blood pressure in their series, which consisted of prisoners was low and differed from that of the wardens whose average value was in better agreement with that of the general population

Various authors (RAGAN & BORDLEY 1941 WENDKOS & ROSSMAN 1943 see Fat Factors) have pointed out that the blood pressure rises with the circumference of the upper arm The increase, if any of the circumference of the upper arm with age in adults is due almost entirely to an increase of the subcutaneous fat The thickness of the subcutaneous fat on the arm was therefore studied for any influence on the correlation between the blood pressure and age After elimination of the influence of the arm fat on the correlation between systolic and diastolic blood pressure respectively and age the correlation coefficients were unchanged for both males (r = + 0 48 and + 0 66** respectively) and females (r = + 0 46 and + 0.36 respectively) which is in agreement with the findings of PICKERING *et al* (1954)

As known, body weight usually increases with age, and in the present investigation the correlation between these two factors was significant for both males and females (r = + 0.51 and + 0.35 respectively) Since individuals with a high body weight usually have a higher blood pressure it was thought that the increase in the blood pressure with age might be related to the increase of body weight with age To check this possibility a partial correlation analysis was done with elimination of the influence of body weight on the correlation between the systolic blood pressure and the diastolic blood pressure, respectively and age No significant decrease of the correlation coefficient was found for the males (r = + 0.30 and + 0.53* respectively) or females (r = + 0 40 and + 0.31 respectively) Thus no evidence was produced for the assumption that the correlation between blood pressure and age was due to increase in body weight with age, which is in agreement with the results obtained by DUNHAM (1927) in males

The values in the different age classes were nearly always somewhat lower for males than for females but the difference between the average systolic blood pressure for males and females was not significant (t = 1 6) The average diastolic blood pressure was, however found to be statistically significantly lower for males than for females (t = 3 0**) The biological background of this difference is receiving attention. The males and the females were not strictly age-matched Thus in the 10—19 year age class the males were relatively evenly distributed within the class, while all the females were 16 years or more This implies that most of the males in this class were still in the stage of development while the development of the females was largely concluded This age class was therefore studied for its effect on the difference in the average diastolic blood pressure between males and females The difference in the average diastolic blood pressure between males and females aged 20—69 i.e after exclusion of those below 20 was not found to be significant (t = 1 9) The difference found by most authors between the blood pressure in males and females (SYMONDS 1923 WETHERBY 1932/33 GOVER 1948, MASTER et al. 1950 HOLMGREN 1955) could thus not be confirmed in the present investigation It is possible that the present series was not large enough to demonstrate any differences in this respect between the sexes

VARIATION OF ARTERIAL BLOOD PRESSURE WITH BODY BUILD

BODY WEIGHT

Judging from the literature, there is certain degree f co-variation between body weight and blood pressure. Many investigators of the correlation between these tw variables have used the body weight as a point of departure. Thus SYMONDS (1923) divided his material according to the build groups of the Medico-Actuarial Mortality Investigation and found that increasing relative body weight was accompanied by an increase in both the systolic and diastolic blood pressures f r all ages in males Largely the same concl sion was arrived at by FABER (1924) for the systolic blood pressure on the basis of an analysis of a series consisting of 1 000 Danish recruits, aged 20 to 25 years, and in 500 "normal" soldiers, aged 18 to 35 years, WENDKOS & ROSSMAN (1943) found an increase of both systolic and diastolic blood pressure with body weight. DUNHAM (1927) found in 8,645 healthy officers, aged 20 t 64 years, a statistically significant correlation between the systolic and diastolic blood pressure, respectively nd body weight and this correlation was not found to be influenced by age. ROBINSON et al. (1939/40) obtained similar results in 478 males and 3 405 females, even after limination of the influence of body height. GOVER (1948) found a signif cant correlation between systolic blood pressure and body weight i 11 490 persons of low-income farm families

The correlation between body weight and arterial hypertension was tudied by HUBER (19??), who of 1,332 healthy men found 1?0 to be o erweight, d of these 10 per cent had arterial hyper tension Among 22 11 rmy officers LEVY et al. (1946) found th t arterial hypertension w more common (ratio 2.5 : 1) in those who were "obese" than in those of normal body weight (BEKN & BECKMAN (1948) noted arterial hypertension in 11.8 pe cent of 1,260 "adipose" patients and some years later in a further 13 4 per cent. In 3? of the 71 patients, who succeeded in reducing their weight, the blood pressure became normal.

In several in estigations the arterial blood pressure was used as a basis in the study of its possible correlation with overweight. MASTER et al. (1953) described 118 males and 51 females with arterial hypertension. Of the males, 32.2 per cent were overweight (10—24 per cent above average) and 6 per cent "obese" (25 per cent or more abov average) while in the controls 14.8 per cent were overweight and 5.3 per cent were bese. The female patients with hypertension did not differ significantly from the controls with respect to overweight + " besity" BECHGAARD s (1945) series consisted of 32? males and 718 females with arterial hypertension. At least 10 kg more than the "ideal weight" was found f r 51.? pe cent f the males and 66.5 per cent of the females and more than 20 kg over weight f 30.5 pe cent f the males and 37.5 per cent of the females Reduction in weight by dieting may produce considerable falls of arterial blood pressure when it was in tially high (TERRY 1923 PREBLE 19?3)

USTVEDT (1933) found no correlation between bod weight and blood pressure in 426 soldiers, aged 21—22 years BOE et al. (19?6) found that the correla tion between body weight and blood pressure was low and that the body weight f person with extremel high blood pressure wa only lightly higher than the average

It is clea from the literature that in most series comprising ubjects f different ges it has been po ible to demonstrate a stati tically significant correla

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Various authors (RAGAN & BORDLEY 1941 WENDKOS & ROSSMAN 1943 see Fat Factors) have pointed out that the blood pressure rises with the circumference of the upper arm The increase, if any of the circumference of the upper arm with age in adults is due almost entirely to an increase of the subcutaneous fat The thickness of the subcutaneous fat on the arm was therefore studied for any influence on the correlation between the blood pressure and age After elimination of the influence of the arm fat on the correlation between systolic and diastolic blood pressure respectively and age the correlation coefficients were unchanged for both males ($r = + 0.48$ and $+ 0.66^*$ respectively) and females ($r = + 0.46^*$ and $+ 0.36^*$ respectively) which is in agreement with the findings of PICKERING et al (1954)

As known body weight usually increases with age, and in the present investigation the correlation between these two factors was significant for both males and females ($r = + 0.51^*$ and $+ 0.35$ respectively) Since individual with a high body weight usually have a higher blood pressure it was thought that the increase in the blood pressure with age might be related to the increase of body weight with age. To check this possibility a partial correlation analysis was done with elimination of the influence of body weight on the correlation between the systolic blood pressure and the diastolic blood pressure respectively and age. No significant decrease of the correlation coefficient was found for the males ($r = + 0.30^{**}$ and $+ 0.53^*$ respectively) or females ($r = + 0.40^*$ and $+ 0.31$ respectively) Thus no evidence was produced for the assumption that the correlation between blood pressure and age was due to increase in body weight with age, which is in agreement with the results obtained by DUNHAM (1927) in males

The values in the different age classes were nearly always somewhat lower for males than for females but the difference between the average systolic blood pressure for males and females was not significant ($t = 1.6$) The average diastolic blood pressure was however found to be statistically significantly lower for males than for females ($t = 3.0$) The biological background of this difference is receiving attention. The males and the females were not strictly age matched Thus in the 10—19 year age class the males were relatively evenly distributed within the class while all the females were 16 years or more This implies that most of the males in this class were still in the stage of development while the development of the females was largely concluded. This age class was therefore studied for its effect on the difference in the average diastolic blood pressure between males and females The difference in the average diastolic blood pressure between males and females aged 20–69 i.e after exclusion of those below 20 was not found to be significant ($t = 1.9$) The difference found by most authors between the blood pressure in males and females (SYMONDS 1923 WETHERBY 1932/33 GOVER 1948, MASTER et al 1950 HOLMGREN 1955) could thus not be confirmed in the present investigation It is possible that the present series was not large enough to demonstrate any differences in this respect between the sexes

still significant for both the systolic and the diastolic blood pressures after elimination of the influence of age. This was also the case for the systolic blood pressure in the females, but the correlation for the diastolic blood pressure and body weight was no longer significant after the elimination of the influence of age.

The difference between the results of USTVEDT (1933) and those obtained in the present investigation regarding the correlation between the systolic blood pressure and body weight for males might be due to the composition of USTVEDT's material being such as not to enable the demonstration of the influence of age. No support for this assumption was found in the present investigation, since the correlation between the systolic blood pressure and body weight for males was still significant after elimination of the influence of age.

The value found for the correlation coefficient between the diastolic blood pressure and body weight was numerically larger for males than for females. The difference between these two correlation coefficients was tested by the t test after the respective values of the correlation coefficients had been converted into z values according to Fisher's Z-table. It was then found that the correlation coefficient for males was probably significantly stronger (t = 2.5) than for females. After elimination of the influence of age on the correlation the

Table 3. *Correlation between diastolic blood pressure and anthropo-somatological factors, calculated partly as total correlation and partly as partial correlation, independent of age.*

Anthropo-somatological factors	Diastolic blood pressure			
	total correlation		partial correlation independent of age	
	males = 85	females = 107	males n = 85	females = 107
Body weight	+ 0.57**	+ 0.32	+ 0.36	+ 0.17
Fat factors				
chin	+ 0.43	+ 0.28	+ 0.13	+ 0.14
back	+ 0.36	+ 0.33	+ 0.09	+ 0.24
sid	+ 0.38	+ 0.33	+ 0.10	+ 0.21
abdomen	+ 0.34	+ 0.31	+ 0.07	+ 0.11
arm	+ 0.18	+ 0.16	+ 0.15	+ 0.10
thigh	+ 0.02	+ 0.23	+ 0.10	+ 0.22
Muscle factors				
handgrip	+ 0.39	= 103 − 0.07	+ 0.32*	n = 104 + 0.08
shoulder pull	+ 0.28	n = 104 − 0.07	+ 0.24	= 104 + 0.02
shoulder thrust	+ 0.23	n = 104 − 0.17	+ 0.23	n = 104 − 0.02
Skeletal factors				
body length	+ 0.32	− 0.09	+ 0.11	− 0.04
radial length	+ 0.26	− 0.17	+ 0.16	− 0.19
tibial length	+ 0.19	− 0.18	+ 0.18	− 0.23
femoral condylar breadth	+ 0.28	+ 0.09	+ 0.19	− 0.01

tion between the arterial blood pressure and body weight.

RESULTS AND COMMENTS

In the present material a significant correlation was found between the systolic and the diastolic blood pressure on one hand, and body weight of both males and females, on the other (Tables 2 and 3 In the evaluation of the correlation between the blood pressure and body weight most investigators have made allowance for the influence of body height In the present investigation the influence of body height on the correlation was studied After elimination of the influence of body height on *the correlation between the systolic and* the diastolic blood pressure, respectively and body weight, these correlations were unchanged for both males (r = + 0.51 + 0.58) and females (r = + 0 40* + 0.31**) This is in agreement with results published by other authors (SYMONDS 1923 FABER 1924 DUNHAM 1927 ROBINSON et al. 1939/40 GOVER 1948)

In a previous section it was shown that the blood pressure in both males and females in the present investigation increased with age Since body weight was also found to vary with age of the males (r = + 0.51**) and of the females (r = + 0.35) it was thought that the correlations between blood pressure and body weight might be due to the influence *of age But this appeared less likely* for the males since the correlation was

Table 2. *Correlation between systolic blood pressure and anthroposomatological factors calculated partly as total correlation and partly as part al correlation, i dependent of ge*

Anthroposomatological factors	Systolic blood pressure			
	total correlation		partial correlation ind pendent of age	
	males n = 85	*f males* n = 107	males n = 85	females n = 107
Body weight	+ 0 52	+ 0 41	+ 0.37	+ 0.35
Fat factors				
chin	+ 0 36	+ 0 44	+ 0 15	+ 0.28
back	+ 0 30	+ 0 50	+ 0 10	+ 0 43
side	+ 0 28	+ 0 51	+ 0 06	+ 0 40
abdomen	+ 0.26	+ 0 37	+ 0 05	+ 0 12
arm	+ 0 14	+ 0 26	+ 0 11	+ 0 20
thigh	+ 0 00	+ 0 17	+ 0 05	+ 0 16
Muscle factors				
handgrip	+ 0 30	n = 104 − 0 11	+ 0 22	n = 104 + 0 09
shoulder pull	+ 0 26	n = 104 − 0 12	+ 0 17	n = 104 − 0 03
shoulder thrust	+ 0 15	n = 104 − 0.25	+ 0 13	n = 104 − 0 07
Skeletal f ctors				
body l ngth	+ 0.21	+ 0 12	+ 0 14	+ 0.22
radial length	+ 0 33	− 0 03	+ 0 27	− 0 05
tibial length	+ 0.28	− 0.05	+ 0 23	− 0 10
femoral condylar breadth	+ 0 34	+ 0 13	+ 0.25	+ 0 01

component f the total body weight that is responsible fo the correlation between blood pressure and body weight and secondly that a correlation has been demonstrated between skinfold thick ness and fat cell number respectively and blood pressure Some authors believe that the correlation found between blood pressure and body fat is due to measurements mad by the auscultatory method being falsely high for persons w th a thick upper arm

RESULTS AND COMMENTS

Th increasing amount of body fat with age has often been described as a contributory factor in the causation of the increase of the blood pressure. In the present material a significant correlation was found between blood pressure and several f the fat factors (Tables 2 and 3) in both sexes

In males the correlation between blood pressure and the thickness of the subcutaneous fat on the trunk (back, side abdomen) was closer than that between the blood pressure and the thickness of the subcutaneous fat on the limbs. The thickness of the fat on the chin wa also found to be significantly correlated with blood pressure which may be explained by the fact that the thickness of the f t at this ite varies more closely with the fat on the trunk than w th that on the limbs (LINDEGÅRD 1956)

In the males in the present material the thickness of the subcutaneous f t on the chin and on the trunk (back, ide, abdomen) increased with ge (= 0.53 + 0.45 + 0.47 + 0 4 respecti ely) while n correlation was found between thickness f fat on the limbs (rm, thigh) (= + 0 10, − 0.08, respectiv ly) and ge Since both the blood pressure and these fat factors which aried w th the blood pressure increased with ge t ppeared possible that the co-variations were due t age

This possibility was checked, and after the elimination f the influence of age on the correlations the latter were no longe found t be significant. The total correlation between the blood pressure and fat f ctors in males agreed well with the result obtained by previous workers in this field such as LINDEGÅRD (1956) WHYTE (1959) and BJURULF (1959) These authors did not eliminate the influence of age on the correlations so that in this respect their results are not comparable with those obtained in th present investigation.

In the females significant correlations were found for the co-variation between the systolic and diastolic blood pressure, on one hand, and the fat on th trunk and the chin, on the other hand (Tables 2 and 3) In addition, the correlation between the yst he blood pressure and the arm fat was significant, and that between the diastolic blood pressure and the thigh fat was probably signif icant. As in th males, a correlation was found between age and f t on the trunk (back, side abdomen) and chin (= + 0.31 + 0.39 + 0.59 + 0.45 respectively) but not for the fat n the limbs (arm, thigh) (= + 0.17 + 0 07 respectively) In view hereof one might suspect that age was partly responsible f r the correlation between blood pressure and the f t f ctors which varied with age This point was checked and numerical reduction was found for the coefficients of all these correla tions on elimination of the influence of ge, and the reduction was most marked f r the correlation between the diastolic blood pressure and the fat factors. The correlations between the systolic blood pressure on one hand, and the fat n the hin, back, side arm (probably significant), on the other hand, were still significant, while the diastolic blood pressure wa only probably ignificantly correlated with the fat on the back, ide and thigh, respecti ly

difference between the correlation coefficients was not significant (t = 1 4)

The background of the correlation demonstrated between the arterial blood pressure and body weight is elucidated further below by an analysis of the correlation between the blood pressure and the main morphological sources of variation of the body weight, namely fat, muscle and skeletal factors

FAT FACTORS

Body fat has often been regarded as that component of the body that is responsible for the correlation between body weight and arterial blood pressure (SYMONDS 1923 PREBLE 1923 FABER 1924 DUNHAM 1927 ROBINSON et al 1939/40 GOVER 1948 and others) By comparison of intra arterial and auscultatory blood pressure recordings it has also been shown that both systolic and diastolic blood pressures recorded are often too high in thick arms and too low in thin arms (RAGAN & BORDLEY 1941) and that a direct correlation is demonstrable between blood pressure and the circumference of the upper arm (WENDKOS & ROSSMAN 1943) A clear correlation (r = + 0 92) has been found between the circumference of the upper arm and body weight (MIALL & OLDHAM 1955) On the basis of the results obtained by RAGAN & BORDLEY PICKERING et al (1954) published tables for correction of blood pressure with respect to arm circumference BØE et al (1956) found the blood pressure to increase slightly with increasing arm circumference After corrections suggested by PICKERING et al the rising tendency was eliminated or even reversed In BJERKEDAL's (1957) series the distribution curves showed that the increase by weight groups of the average blood pressure values was the result of a small addition to the blood pressure value common to all individuals in connection with an increase of body weight. The apparent increase of the measured auscultatory values of the arterial blood pressure with increasing circumference of the upper arm because of increasing body fat was regarded as sufficient to explain the correlation between body weight and arterial blood pressure

By measurement of the thickness of the skinfold a measure was obtained of the fat factor With this technique LINDEGÅRD (1957) found in a series consisting of 58 men, 20 to 30 years of age that the fat on the abdomen was *significantly* correlated with both the systolic and the diastolic blood pressure (r = + 0 42 * and + 0 44** respectively) WHYTE (1959) who used the sum of the fat on the back, abdomen and arm as a measure of fatness, arrived at similar conclusions in a series consisting of 100 men 20 to 40 years of age.

BJURULF (1959) studied the subcutaneous fat at necropsy of 106 males in Lund The thickness of the subcutaneous tissue in the mid axillary line at the level of the xiphoid process, lateral to and below the umbilicus as well as the ventral thigh above the patella were measured and representative blood pressure recordings in these individuals were obtained from the files of the University Hospital Lund *Statistical analysis showed that the fat* thickness was significantly correlated with the systolic blood pressure (r = + 0.26) and probably significantly with diastolic blood pressure (r = + 0.22*) The residual F fat thickness (cell size) which reflects the number of cells in the fat tissue, was probably significantly correlated with the systolic blood pressure and the diastolic blood pressure (r = + *0.23 and* + *0.22* respectively) The cell size of the fat tissue was not significantly correlated with the systolic or the diastolic blood pressure.

It is thus clear from the literature that body fat has been regarded as that

Neither did the empirical regression line of the diastolic blood pressure on back fat in the females (Fig 6) differ essentially from the theoretical regression line The mean diastolic blood pressure in the back f t lass 20—24 mm is somewhat too low but it is based n only 6 bservations The scatter diagram for the correlation between the diast lic blood pressure and back fat bows that the plottings are well crowded around the regression line. There ppears t be no extreme variants with marked influence on the correlation coefficient.

Th empirical regression lines of the systolic blood pressure and the diastolic blood pressure, respectively on the side fat in females (Figs 7 and 8) closely follows the theoretical regression lines The scatter diagrams illustrating the co-variation between the systolic and diastolic blood pressure, on one hand, and the side fat, on the other show that the plottings are well crowded around the respective regression lines. There appears to be no extrem variants capable of unduly influencing the cor relati n coefficient.

As mentioned above, several uthors (RAGAN & BORDLEY 1941 WENDKOS & ROSSMAN 1943 BOE et al. 1956, BJERKEDAL 1957) claim that the correlation between the blood pressure and the increased amount of body fat is due to the falsely high blood pressure recordings

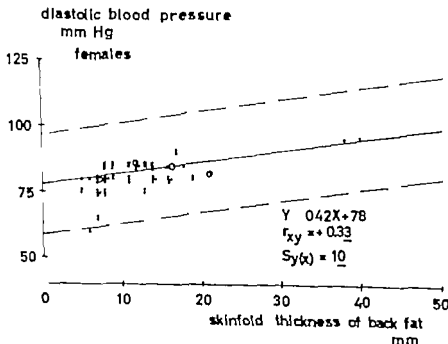
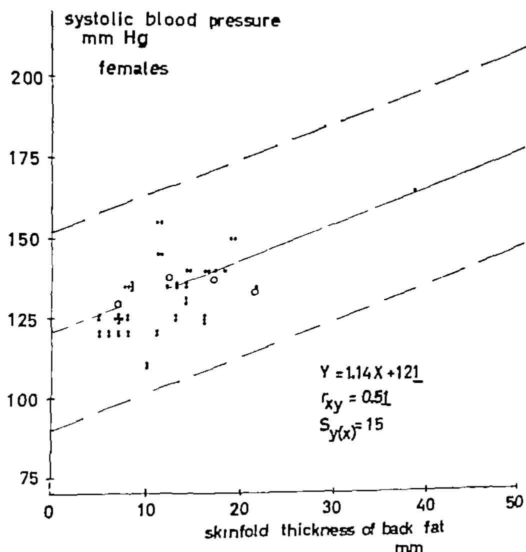


Fig. 6. Scatter diagram of correlation between the diastolic blood pressure (Y) and skinfold thickness of back fat (X) in females. The continuous line denotes the theoretic regression line of the diastolic blood pressure on back fat. The interrupted lines denote the distance of twice the standard deviation from the regression line The circles indicate the arithmetic mean of the diastolic blood pressure in consecutive back fat classes.

The scatter diagram and the regression e of the systolic blood pressure on infold thickness of the back fat in nales are given in Fig 5 The empirical gression line i.e the imaginary line ning the arithmetic means of the stolic blood pressure in the different asses of skinfold thickness of the back : does not differ substantially from e theoretical regression line The mean systolic blood pressure in the back fat class 20—24 mm is somewhat too low but it is based on only 6 observations The scatter diagram of the correlation between the systolic blood pressure and back fat showed that the plottings were well crowded around the regression line. There appears to be no extreme variants with a marked influence on the correlation coefficients



5 Scatter diagram of correlation between the systolic blood pressure (Y) and skinfold thickness of b fat (X) in females. The continuous line denotes the theoreti regression line of the systoli blood ssure on back fat. The interrupted lines denote the distance of twice the standard deviation from the ression line. Th circles indicate the rithmeti mean of the systolic blood pressure in consecutive back classes

N ithe did the empirical regression line of the diastolic blood pressure on back fat in th females (Fig 6) differ essentially from th theoretical regress ion line. The mean diastolic blood pressure in the back fat class 20—24 mm. is somewhat too low but it is based on only 6 observations The scatter diagram f the correlation between the diast lic blood pressure and back fat hows that the plottings are well crowded round the regression line. There appears to be no extreme variants with a marked influence on the correlation coefficient.

The empirical regression lines of the systolic blood pressure and th diastolic blood pressure, respectively on the side fat in females (Figs. 7 and 8) closely follows the theoretical regression lines. The scatter diagrams illustrating the co-variation between the systolic and diastolic blood pressure, on ne hand, and the side fat, on the other show that the plottings are well crowded around the respective regression lines There appears to be no extreme variants capable of unduly influencing the correlation coefficient.

As mentioned above, several authors (Ragan & Bordley 1941, Wendkos & Rossman 1943, Boe et al. 1956, Hiebekedal 1957) claim that the correlation between the blood pressure and the increased amount of body fat is due t the falsely high blood pressure recordings

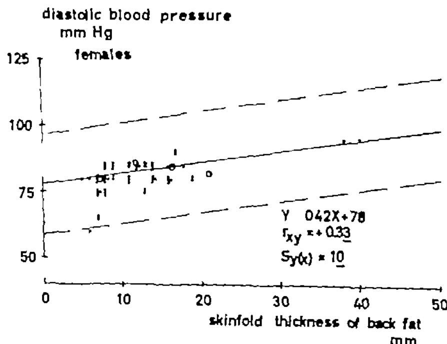


Fig. 6. Scatter diagram of correlation between the diastolic blood pressure (Y) and skinfold thickness of back fat (X) in females. The continuous line denotes the theoretic regression line of the diastolic blood pressure on back fat. The interrupted lines denote the distance of twice the standard deviation from the regression line. The circles indicate the arithmetic mean of the diastolic blood pressure in consecutive back fat classes.

The scatter diagram and the regression line of the systolic blood pressure on skinfold thickness of the back fat in females are given in Fig 5 The empirical regres ion line i e the imaginary line joining the arithmetic means of the systolic blood pressure in the different classes of skinfold thickness of the back fat does not differ substantially from the theoretical regression line The mean systolic blood pressure in the back fat class 20—24 mm is somewhat too low but it is based on only 6 observations The scatter diagram of the correlation between the systolic blood pressure and back fat showed that the plottings were well crowded around the regression line. There appears to be no extreme variants with a marked influence on the correlation coefficients

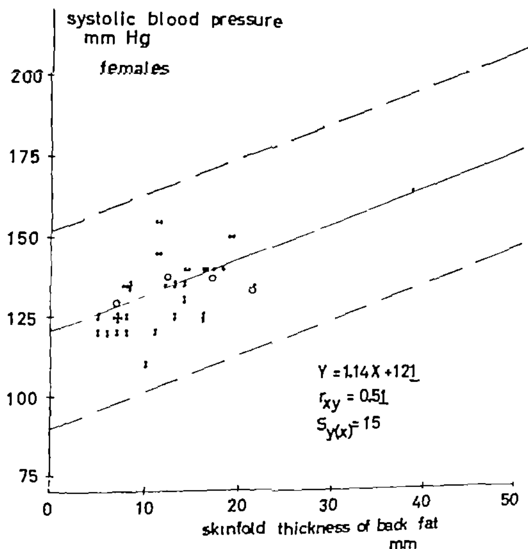


Fig 5. Scatter diagram of correlation between the systolic blood pressure (Y) nd skinfold thickness of back fat (X) in females. The continuous line denotes the theoretic regression line of the systolic blood pressure on back fat. The interrupted lines denote the distance of twice the standard deviation from the regression lin The circles indicate the arithmetic mean of th systolic blood pressure in consecutive back fat classes

with increasing thickness of the upper arm, when the pressure is measured by the auscultatory method. This source f error can influence the above-mentioned correlations between blood pressure and fat on the trunk only if there is a correlation between f t on the arm and fat on the trunk. In a series f 320 Swedish 20 year old army men LINDEGÅRD (1956) found a significant correl tion between fat on the arm and fat n the back and on the side, respectively (r = + 0.61 and + 0.59 * respectively). For the females in the present investigation the correlations between the fat on the arm and fat n the back and on the side, respectively were significant (= + 0.62 and + 0.56) and the correlations persisted after elimination of the influence of age (r = + 0.56 and + 0.57) It w against this background that the females were studied f the influence of arm fat on the correlation between blood pressure and fat on th back and on the side, respectively independent of age After elimination of the influence f fat on the arm, the correlations between the systolic blood pressure and fat n the back and on the side, respectively

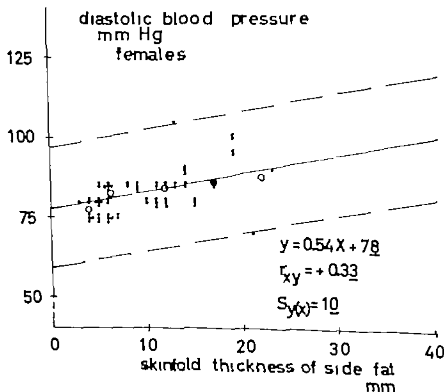


Fig. 8. Scatter diagram of correlation between the diastolic blood pressure (Y) and skinfold thickness of side fat (X) in females. The continuous line denotes the theoretic regression line of the diastolic blood pressure on side fat. The interrupted lines denote the distance of twice the standard deviation from the regression line. The circles indicate the arithmetic mean of the diastolic blood pressure i consecutive side fat classes.

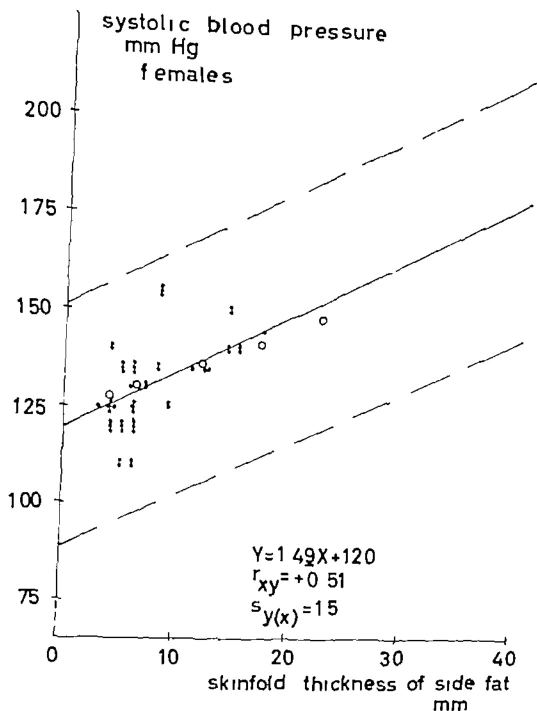


Fig. 7 Scatter diagram of correlation between the systolic blood pressure (Y) and skinfold thickness of side fat (X) in females. The continuous line denotes the theoretic regression line of the blood systolic pressure on side fat. The interrupted lines denote the distance of twice the standard deviation from the regression line. The circles indicate the arithmetic mean of the systolic blood pressure in consecutive side fat classes.

with increasing thickness of the upper arm, when the pressure is measured by the auscultatory method. This source f error can influence the above-mentioned correlations between blood pressure and fat on the trunk only if there is a correlation between fat on the arm and fat on the trunk. In series of 320 Swedish 20 year old army men LINDEGÅRD (1956) found a significant correlation between fat on th arm and fat on the back and on the side, respectively (= + 0.61 and + 0.59 respectively) For the females in the present investigation the correlations between the fat on the arm and f t on the back and on the s de, respectively were significant (r = + 0.62 and + 0.56) and the correlations persisted after elimination of the influence of age (r = + 0.56 and + 0.57) It was against this background that the females were studied f r the influence f arm fat on the correlation between blood pressure and fat on the back and on the side, respectively independent f age After elimination of the influence of fat on the arm, the correlations between the systolic blood pressure and fat on the back and on the side respectively

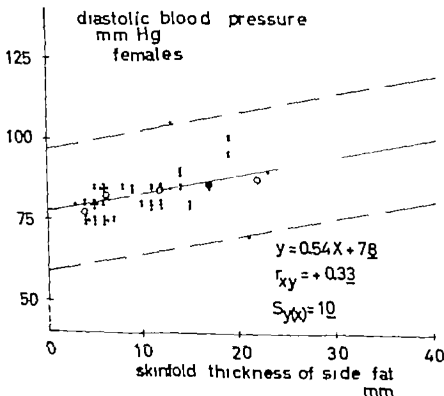


Fig. 8. Scatter diagram of correlation between the diastolic blood pressure (Y) and skinfold thickness of side fat (X) in females. The continuous line denotes the theoretic regression line of the diastolic blood pressure on side fat. The interrupted lines denote the distance of twice the standard deviation from the regression line. The circles indicate the arithmetic means of the diastolic blood pressure in consecutive side fat classes.

independent of age, were unchanged (r = + 0.39 * and +0.35) and no definite change in the correlations between the diastolic blood pressure and fat on the back and side, respectively independent of age were demonstrable (r = + 0.22* and + 0 18) The findings thus failed to support the hypothesis of RAGAN & BORDLEY

MUSCLE FACTORS

The influence of the muscle factor on arterial blood pressure has been studied by RUSSO (1953) who examined 2 410 men aged 20 to 30 years The vigorous men of average height with well developed muscles had the highest systolic blood pressure The short, robust men with well developed muscles had a somewhat increased systolic blood pressure and the highest diastolic blood pressure

In LANGE ANDERSEN & ELVIK s investigation (1955) 377 athletes were compared with 652 non athletes They *found that the systolic and diastolic* blood pressures were significantly lower in athletes than in non athletes

As a measure of the muscle factor LINDEGÅRD (1957) used the gross muscular strength of the shoulder pull as judged by dynamometric recordings In a series consisting of 58 men, aged 20 to 30 years no correlation could be found between this muscle factor and the blood pressure

Summarizing it may be said that no significant correlation could be found between objective recordings of the muscle factor and the blood pressure

RESULTS AND COMMENTS

In the evaluation of results in which the muscle factor is included allowance must be made for the fact that the muscle factor changes with age If a given series includes individuals from 20 years of age and more, it must be borne in mind that in males the amount of muscles decreases with increasing age (BJURULF 1959) In the present investigation the handgrip recordings were also found to vary inversely with age in 20—68 year old *males (r = — 0.30**)* while no such correlation could be demonstrated between the shoulder pull and shoulder thrust, respectively and age (r = —0 03 and —0 13 respectively)

In the 20—29 year class the arithmetic means found for the different muscle factors were in the main higher than in the other age classes which suggests that muscle mass increased between 10 and 29 years The variation of the different muscle factors with age was also studied for the age groups 10—19 years and 20—29 years, separately It was found that the correlation coefficients for the relationships between age and handgrip shoulder pull and shoulder *thrust,* respectively *were considerably* higher in the 10—19 year age class (r = + 0.81** + 0.81 + 0 78 *) than in the 20—29 year age class (r = + 0.37 + 0.38 + 0 09) This suggests that the increase occurred mainly in the 10—19 year interval.

For the females in the present material a negative correlation was found between handgrip shoulder pull and shoulder thrust, respectively and age (r = — 0.36 — 0.21 — 0 40* respectively) and these correlations persisted when calculated for the age classes 20—69 years only (r = — 0 44* — 0 1 — 0.38 respectively) possibly because all of the females were 16 years of age or more.

For males, 10 to 68 years of age, several significant correlations were found between the blood pressure and the muscle factors (Tables 2 and 3) The correlations with systolic blood pressure were found to be due to a large extent to the influence of age, for after elimination of the influence of age the correlation between *the systolic* blood pressure and the handgrip was only probably significant The influence of

age on the correlation between diastolic blood pressure and muscle factors did not appear to be so marked, for after elimination of the influence f age on the co-variation, the correlations with the handgrip were still significant, and with the shoulder pull and shoulder thrust, probably significant.

Since the muscle factor in the 10—19 year age class differed from that in the 20—69 year classes, the 20—68 year old males were also studied separately for any correlation between blood pressure and muscle factors. It was found that the correlations dem nstrated above were due in the main to the 10—19 year age class. Thus, no significant correlation could be f und in the 20—69 year age classes for syst lic blood pressure r diastolic blood pressure, and the correlation coefficients (r) for the handgrip were + 0.03 and — 0 07 respectively for shoulder pull + 0 04 and + 0.05 respectively and fo shoulder thrust — 0.01 and + 0.04 respectively which agrees with the findings of LINDEGÅRD (19₅6) and HJORTH (1959). The differ ences between results obtained in the present investigation and those published by RUSSO (19₅3) and LANGE ANDERSEN & ELVIK (19₅5) may be due to the fact that in the present investiga tion the muscle factors were assessed by the dynamometric technique, but by subjective evaluation by the thors just mentioned

As mentioned above, the strength f the ha dgrip decreased with advancing ge in the 20—69 year classes, which might conceal a correlation between blood pressure and handgrip Elimina tion of the influence of the age on the correlation between the systolic blood pressure and the diastolic blood pressure, respectively and handgrip shoulder pull and houlder thrust, respectively ga no substantial effect on the correlation coefficient which remained non-significant (r = + 0.16 and + 0 12, + 0 06 and + 0 07 + 0.04 and + 0 0 respectively)

The only correlation found between blood pressure and muscle factors for females (Tables 2 and 3) consisted of a probably significant negative correla tion between the systolic blood pressure and the shoulder thrust. Since the muscle factors for the females decreased with age and that the systolic blood pressure increased with age, it was thought that the negative correlation between the systolic blood pressure and shoulder thrust was due to age After elimination of the influence of age on the correlation the latte was not significant.

LENGTH AND STURDINESS FACTORS OF THE SKELETON

N clear-cut relationship has hithert been found between stature and blood pressure (FABER 1924 HUBER 1927 ALVAREZ & STANLEY 1930 USTVEDT 1935 GOVER 1948, MASTER et al 1950 and BØE et al. 1956)

Body height is dependent on both the length factor and the sturdiness factor of the skeleton (LINDEGÅRD 19₅3) In 58 males, aged 20—30 years, no correlation was found by LINDEGÅRD (19₅7) between the skeletal length factor (tibial length) and blood pressure, but *significant negative correlation* was demonstrated between sturdiness factor (femoral condylar breadth) and the systolic blood pressure but not with the diastolic HJORTH (1959) also found no correlation between the tibial length and the blood pressure in 110 males, aged 25 to 88 years, but he was unable to confirm the correlation with the stur diness factor

It is clear from previous in estigations that no correlation has been found between blood pressure and keletal factors with the exception of the signif icant negative correlation demonstrated by LINDEGÅRD between the syst lic blood pressure and turdiness factors

RESULTS AND COMMENTS

Body height was included in the present investigation in spite of the fact that it is not a skeletal *dimension only* and that it includes both the length factor and the sturdiness factor. The reason why this body dimension is often used in such studies, is probably that it can be measured easily with fairly good accuracy. As in investigations by other workers in this field (FABER 1924, HUBER 1927 and others) hardly any correlation was found between body height and blood pressure (Tables 2 and 3). Thus in males the correlations between body height, on one hand, and systolic or diastolic blood pressure on the other hand, were found to be probably significant and these weak correlations proved to be due to the influence of age. No significant correlation could be found for females in this respect but a probably significant correlation was found for the correlation between systolic *blood pressure and body height after* elimination of the influence of age. Since no correlation could be found between the systolic blood pressure and the two skeletal factors representing the most variable sources of body height it appeared likely that this probably significant partial correlation found *between systolic blood pressure and body* height, independent of age was due to chance.

Co-variations were found between the pure skeletal factors (radial and tibial length and femoral condylar breadth) and blood pressure for males aged 10–68 years (Tables 2 and 3). The correlation was numerically stronger for the systolic than for the diastolic blood pressure and persisted even after elimination of the influence of age on the correlation which was not the case with the diastolic blood pressure.

Since it might be expected that in males aged 10 to 19 the skeletal factors differ from those aged 20–68 years, the latter were studied separately for any correlation between the skeletal factors and the blood pressure.

The effect of the 10–19 year age class was so strong that, after elimination of this effect on the entire series, the correlation between the systolic and diastolic blood pressure respectively and the skeletal factors for males aged 20 to 68 years was no longer significant, *the correlation coefficients (r) then being* + 0.20 and + 0.04 for radial length, + 0.22 and + 0.08 for tibial length and + 0.19 and + 0.02, respectively for femoral condylar breadth. In agreement with results obtained by LINDEGÅRD (1957) and BJURULF (1959) no correlation was found between the length *factor and the blood pressure*. Like BJURULF (1959) and in contrast to LINDEGÅRD (1957) in the present material no correlation was found between the systolic blood pressure and the sturdiness factor. After elimination of the influence of age on the correlation between blood pressure and radial length the coefficients were + 0.22, + 0.0[illegible] for tibial length + 0.25*, + 0.16 and for femoral condylar breadth + 0.20, + 0.07 respectively. These values for the correlation coefficients may suggest a certain positive correlation between the systolic blood pressure and the skeletal factors.

As for the females (Tables 2 and 3) no correlation could be found primarily between the blood pressure and the skeletal factors but it was found that the influence of age masked a certain correlation between the length factors and the diastolic blood pressure. After elimination of the influence of age a *probably significant* negative correlation was found for both the radial length and the tibial length respectively and the *diastolic blood pressure*.

DIFFERENTIAL STATISTICAL ANALYSIS OF THE CORRELATION BETWEEN ARTERIAL BLOOD PRESSURE AND BODY WEIGHT

Overweight, which has been calculated in different ways, has been ascribed to increased amount of body fat. As mentioned previously in SYMONDS (1923) FABER (1924) and in ROBINSON's et al. (1939/40) material the effect of stature on the correlation between body weight and arterial blood pressure was to a certain extent eliminated and a co-variation was found between blood pressure and body weight, independent of body height. The significant correlation found by GOVER (1948) between the systolic blood pressure and body weight persisted, when height was held constant. Neither could MASTER et al. (1950) find any influence of body height on the correlation between body weight and systolic and diastolic blood pressure, respectively. On statistical analysis of the correlation between blood pressure and body weight in 100 men, aged 20 to 40 years, WHYTE (1959) found that even when age, height, subcutaneous fat and size of the arm were kept constant, a significant correlation still existed between blood pressure and body weight.

It is thus clear from the literature that body fat is usually regarded as the most important component of body weight responsible for the variation of the latter with blood pressure. In an investigation where skinfold thickness was used as a measure of the fat factor however body fat was not found to have any influence on the correlation between blood pressure and body weight. Neither was body height found to have any effect on the correlation between body weight and blood pressure.

RESULTS AND COMMENTS

The inter-individual variation of body weight is due in the main to variations in the amount of fat, musculature, skeleton, inner organs and body fluid. The intra-individual variations in change of body weight with age in adults is due mainly to variation of the amount of fat, musculature and body fluid. As a basis for a biological evaluation of the above-mentioned correlations between arterial blood pressure and body weight, the correlations were calculated between blood pressure and the main sources of morphological variation of the intra-individual and inter individual variation of body weight, namely fat, muscle, length and sturdiness factors.

SYSTOLIC BLOOD PRESSURE

For the males a significant correlation between the systolic blood pressure and body weight was still demonstrable even after elimination of the influence of age (Table 2), which is in agreement with the results of DUNHAM (1925) and ROBINSON et al. (1939/40). Since it had been shown that blood pressure varied with muscle and skeletal factors, respectively it was investigated to what extent these were responsible for the correlations between body weight and blood pressure. Of the muscle factors, the handgrip was the only one that could plausibly have any influence on the correlation between the systolic blood pressure and body weight, independent of age (Table 2), since *no* correlation had been found between the other two muscle factors and the systolic blood pressure after elimination of the influence of age. After elimination of the influence of *handgrip* on the correlation between the systolic blood pressure and body weight, independent of age, a numerical reduction was obtained of the correlation coefficient but the correlation was still significant ($= + 0.31$).

After elimination of the influence of body height on the correlation between the systolic blood pressure and body

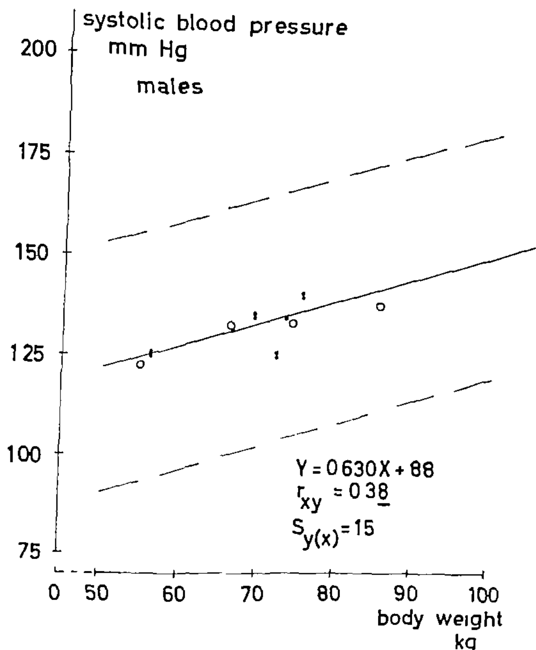


Fig 9 Scatter diagram of correlation between systoli blood pressure (Y) and body eight (X) f m les aged 20 to 68 years. Th continuous line denotes th theoreti regression lin of th systoli blood pressure on body weight. Th interrupted lines denote the distance of twice the standard deviation from the regression line. Th circles indicate th arithmetic mean of the systolic blood pressure i consecutive body w ights classes.

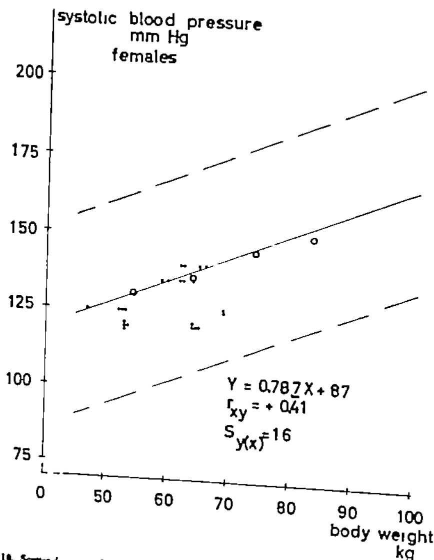


Fig 10. Scatter diagram of correlation between systolic blood pressure (Y) and body weight (X) for females. The continuous line denotes the theoretic regression line of the systolic blood pressure on body weight. The interrupted lines denote the distance of twice the standard deviation from the regression line. The circles indicate the arithmetic mean of the systolic blood pressure in consecutive body weight classes.

weight independent of age the coefficient for the correlation was unchanged ($r = +0.36^{**}$) while a numerical reduction was obtained for the correlation coefficient after elimination of the radial length, tibial length, and femoral condylar breadth respectively ($r = +0.25^{*}$ $+0.29^{**}$ $+0.25^{*}$)

Since, as pointed out above a difference could be expected between the 10—19 and the 20—69 year age classes it was investigated whether the correlation between the systolic blood pressure and body weight was due to the influence of the 10—19 year age class It was found that the systolic blood pressure and body weight for the 20—69 year age classes was significantly correlated ($r = +0.38^{**}$) and that after elimination of the influence of age this correlation was $r = +0.31^{**}$ This correlation was not tested for the influence of the correlation between the systolic blood pressure and handgrip radial length and femoral condylar breadth respectively independent of age on it, because the last mentioned correlation was not significant ($r = +0.16$ $+0.22$ $+0.20$ respectively) for the 20—68 year group On the other hand the influence of the correlation between the systolic blood pressure and tibial length, independent of age, was studied Elimination of this influence gave the partial correlation between systolic blood pressure and body weight for 20—68 year old males, independent of age and tibial length and this partial correlation was probably significant ($r = +0.27^{*}$) The results found for males regarding the correlation between systolic blood pressure and body weight agree with those accounted for by WHYTE (1959) though the body dimensions, whose influence on the above-mentioned correlations was studied, are not strictly comparable

The regression of the systolic blood pressure on body weight for males, aged 20—68 years, was studied (Fig 9) It was found that the arithmetic means of the systolic blood pressure in the different weight classes, i.e the empirical regression line, closely followed the theoretical regression line. The scatter diagram of the co-variation between the systolic blood pressure and body weight showed that the plottings crowded fairly well around the theoretical regression line and no extreme variants with an undue influence on the correlation and regression coefficients were observed

For females the correlation between the systolic blood pressure and body weight was still significant after elimination of the influence of age which is in agreement with ROBINSON et al. (1939/40) In view of the fact that several fat factors were closely correlated with the systolic blood pressure even after the influence of age had been eliminated (Table 2) it was thought that the fat factors might have been responsible for the correlation found between the systolic blood pressure and body weight. Since the back fat and the side fat were the fat factors that showed the strongest correlation with the systolic blood pressure after the elimination of the influence of age the partial correlations were calculated between systolic blood pressure and body weight independent of back fat and age, and of side fat and age and they were found to be not significant ($r = +0.09$) and probably significant ($r = +0.22$) respectively

The regression of systolic blood pressure on body weight was also studied for females (Fig 10) The arithmetic means of the systolic blood pressure in the different weight classes, i.e the empirical regression, fitted the theoretical well. The scatter diagram of the co-variation between systolic blood pressure and body weight showed that the plottings were crowded around the theoretical regression line, and no

extreme variants with undue influence on the correlation and regression coefficients could be seen.

DIASTOLIC BLOOD PRESSURE

The correlation between the diastolic blood pressure and the body weight f the males (Table 3) was still significant after elimination of the influence of age, which grees with the findings of DUNHAM (1925) and ROBINSON et al. (1939/40) The body dimension probably responsible f this correlation might be the muscle factor because it was significantly correlated with the dia stolic blood pressure even after elimina tion of the influence of age. The significance of the muscl factor for the correlation between the diastolic blood pressure and body weight, independent of age, was studied by eliminating the influence of the respective muscl factors. This gave partial correlations between the diastoli blood pressure and the body weight, independent of age and handgrip shoulder pull and shoulder thrust, respectively The coefficients for these partial correlations were + 0.15 + 0..8 and + 0.30 Since the hand grip is th only muscle facto that had any substantial influence on the cor relation between th diastolic blood pressure and body weight, independent of age, the demonstrated influence of the handgrip might have been due to chance.

It was considered possible that the ge class 10 -19 years was responsible for that part f the correlation between the diastolic blood pressure and body weight that persisted after elimination of the influence of age This was checked by calculations based on the 20—69 year age classes. The correlation between the diastolic blood pressure and body weight, independent of age, was then probably significant (r = + 0.24) After elimination of the influence of handgrip, houlder pull and shoulder thrust, respectively on this correlation no significant decrease was found (r = + 0.21, + 0.23 + 0.23 respectively) Neither could WHYTE (19 9) find any influence with certainty on the correlation between the diastolic blood pressure and body weight f the body variables studied.

Th regression of the diastolic blood pressure on body weight was studied for males, aged 0—68 years (Fig 11). It was found that the arithmetic means of the diastolic blood pressure in the different weight classes, *i.e* empirical regression line, closely resembled the theoretical The scatter diagram showed that the plottings were well crowded around the theoretical regression line and no ex treme variants capable of unduly influencing the correlation and regression coefficients could be found.

The body weight of the females showed no significant correlation with the blood pressure after elimination f the influence of age (Table 3) It was, however found that the correlation was masked by the fa t that in the females the skeletal length factor was negatively correlated with age After elimination of the influence of the radial length and the tibial length, respectively on the correlation between the diastolic blood pressure and body weight, independent of age, a significant correlation (r = + 0.31 and + 0.2. respectively) was f und for these partial correlations of diastolic blood pressure on body weight, independent of radial length and ge, and f tibial length and age, respectively

Summing up the findings thus howed that in males the *correlation between* the *systolic blood* pressure and body weight could not be ascribed t any body *dimensions* studied (fat, muscle and keletal factors) o to the age class 10—19 years. The significant correlation found for the females was, however apparently due mainly to the fat factors.

The correlation found for males between diastolic blood pressure and body weight appears to be due mainly to the individuals in the 10–19 year age class. This correlation did not appear to be influenced by any of the other body dimensions studied. The demonstrated influence of handgrip on the correlation may have been due to chance. For females the skeletal length factor appeared to mask a correlation between diastolic blood pressure and body weight.

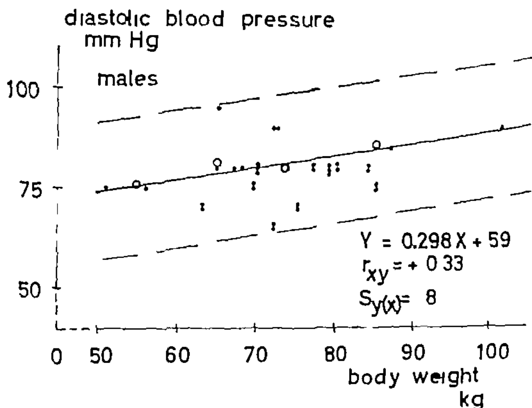


Fig. 11 *Scatter diagram of correlation between diastolic blood pressure (Y) and body weight (X) for males aged 20 to 68 years. The continuous line denotes the theoretical regression line of diastolic blood pressure on body weight. Interrupted lines denote twice the standard deviation from the regression line. The circles indicate the arithmetical mean of the diastolic blood pressure in consecutive body weight classes.*

VARIATION OF ARTERIAL BLOOD PRESSURE WITH PLASMA LIPIDS

The correlation between the arterial blood pressure and the blood lipids has been the subject of many investigations. In previous publications in this field interest has been focused mainly on the cholesterol. Since the elaboration f methods for separating and measuring the blood lipid components, the latter have been studied fo any correlation with the arterial blood pressure. In the present investigation attention was given to the total lipids and the lipoprotein fractions separable by paper electrophoresis.

Investigation of the correlation between the arterial blood pressure and the total serum lipids have given divergent results. Thus WACKER & FAHRIG (1932) found persons with "essential hyper tension" to have a higher average total serum lipid level than persons with a normal blood pressure. It should how ever be pointed out that of the 19 controls with normal blood pressure in the last-mentioned study 15 were below 30 years and the oldest was 46 years, while of the 12 individuals who had hypertension, one was 47 years and most of the remainder above 60 years. But also HARRIS et al. (1949) found that the total serum lipids were significantly higher in persons with hypertension than m ge-matched controls

Other uthors have, howeve n t been able t show any correlation between the serum lipids and the blood pressure Thus PAGE et al. (1936) and FISHBERG (19 4) found the serum lipids t be within the normal range in patients with hypertension. Simila results have been obtained by HATCH & KENDALL (1932) and HATCH t al. (1955) on comparison between 40 and 41 patients, respectively with severe hypertension and healthy subjects f the sam ages. Neither in series in which males and females were studied separately ha it been possible to demonstrate any difference in serum lipids between individuals with and without hypertension (WARIS 1958)

On investigation of the correlation between the concentration of the β-lipoproteins in the serum, as determined by ultracentrifugal analysis and the blood pressure, LEWIS & PAGE (1953) found the β-lipoproteins in 27 patients with mild hypertension to be normal Similar results in patients with hyper tension have been described by CORCORAN t al. (1957)

As for the concentration of the lipoproteins determined by ultra centrifugal analysis, LEWIS & PAGE (1953) found normal values in 27 individuals with mild hypertens on. When different age groups of males and females were studied, WARIS (1955) found that females with hypertension in the 41—50 year age classes had, on the average a higher percentage of -lipoproteins as determined by paper electrophoresis than females with a normal blood pressure N difference could be demonstrated for the other age classes. As for the males, no such difference could be found in any age class.

BERKOWITZ (1961) studied the correlation between th blood pressure and the fat tolerance curve, as measured by loading with isotopic triolein in 50 patients, ged 29—63 years, with arterial hypertension. On oral administration of the f t he found an impaired fat tolerance curve for 72 per cent, and for 6 per cent on intravenous administration.

Some authors have been able to d monstrat a correlation between the total serum lipids and the blood pressure which thers have not. N co-variation has been found between the β- or -lipoproteins and the blood pressure An impaired fat tolerance curve has,

however been demonstrated for patients with arterial hypertension

RESULTS AND COMMENTS

PLASMA LIPIDS IN FASTING STATE

Several of the plasma lipids varied with the arterial blood pressure, and particularly with the diastolic blood pressure, in both sexes (Tables 4 and 5) In the present investigation the males as well as the females were studied for any variation of the plasma lipids with age In both males and females a correlation was found between age and total lipids (r = + 0.51 and + 0.55 * respectively) chylomicrons (r = + 0.33 * and 0.26 * respectively) and β lipoproteins (r = + 0 46** and + 0.58 * respectively) but not for α lipoproteins Those plasma lipids that varied significantly with the blood pressure, thus increased with increasing age Since the arterial blood pressure also increased with age, it was thought that this co variation might produce an apparent correlation between the plasma lipids and the blood pressure The influence of age on the correlations were therefore eliminated, after which the correlations for the males were no longer significant. This indicates that the variation of the two factors with age were probably at least partly responsible for the correlation.

As for the females, the correlation coefficients were found to be numerically lower after elimination of the influence of age. The correlation between systolic blood pressure and the fasting value of the total lipids was, however still probably significant, and that between the diastolic blood pressure and the fasting value of the total lipids was significant. The β-lipoproteins showed largely the same variation pattern with the blood pressure as did the total lipids No correlation could be demonstrated between the blood pressure and chylomicrons or the α lipoproteins. This suggests that the β-lipoprotein fraction was the one responsible for the correlation in both cases This assumption was also supported by the fact that no significant correlation was demonstrable (r = − 0 00 and + 0 08, respectively) after elimination of the influence of the β-lipoproteins on the partial correlations between the fasting value of the total lipids and the systolic and diastolic

Table 4. *Correlation between the systolic blood pressure and plasma lipids in fasting state and after fat ingestion, calculated partly as total correlation and partly as partial correlation independent of age*

Plasma lipids	*Systolic blood pressure*			
	total correlation		partial correlation independent of age	
	males n = 85	*females* n = 107	*males* n = 85	females n = 107
Fasting value				
total lipid	+ 0 19	+ 0 43	− 0.08	+ 0.22
chylomicrons	+ 0.29	+ 0 16	+ 0 16	+ 0 04
β-lipoproteins	+ 0 13	+ 0 46	− 0 17	+ 0.21
α-lipoproteins	− 0 06	+ 0 01	− 0 02	+ 0 01
Increase 3-hours after fat ingestion				
total lipids	+ 0 03	+ 0 14	+ 0 02	+ 0 02
chylomicrons	− 0 07	+ 0 06	− 0 08	+ 0 03
β-lipoproteins	+ 0 09	+ 0 12	+ 0.07	− 0.01
α-lipoproteins	− 0 04	+ 0.21	− 0.06	+ 0.18

blood pressure, respectively independent of age

The regression of the systolic and diastolic blood pressure, respectively on the fasting value of the ß-lipoproteins in females was studied (Figs 12 and 13). The empirical regression lines for the systolic and the diastolic blood pressure, respectively on the ß-lipoproteins fitted the theoretical regression line for the respective correlation well. In the scatter *diagrams f the correlation between the* systolic blood pressure and the diastolic blood pressure, respectively and the ß-lipoproteins the values crowded around the respective regression lines, and no extreme variants unduly influencing the respective correlation and regression coefficient could be seen.

In addition, it was tested whether the correlation between the ß-lipoproteins and blood pressure in the females could be ascribed to the co-variation of any of these variables with the fat fact r. It was found that the correlations between the systolic blood pressure and *the ß-lipoproteins, independent of back* fat and side fat, respectively were significant (r = + 0.38 and + 0.32 respectively) and the correlations between the systolic blood pressure and ß-lipoproteins, independent of back fat and age, were probably significant (r = + 0.21) and independent f side f t and age, respectively not significant (r = + 0.17). The correlation between the diastolic blood pressure and ß-lipoproteins was studied in the same way. After elimination of the influence of back fat the correlation was still significant (= + 0.41) as well as after the *elimination f side fat (r = + 0.39)*. The influence of age on these partial correlations was also studied, and the partial correlation thereby btained between the diastolic blood pressure and ß-lipoproteins, independent of back fat and age, and of side fat and age, respectively also proved significant (r = + 0.31 and + 0.29 respectively).

The correlation between systolic blood pressure and ß-lipoproteins thus ppears t be due in the main to the variation of these factors varying with age, and no influence of the fat factors could be *demonstrated with certainty. The in*fluence of age was numerically less for the correlation between the diastolic blood pressure and the ß-lipoproteins,

Table 6 Correlation between the diastoli blood pressure and plasma lipids in fasting state and after fat ingestion, calculated partly as total correlation and partly as partial correlation independent of age.

Plasma lipids	Diastolic blood pressure			
	total correlation		partial correlation independent of age	
	males = 85	females = 107	males n = 85	females = 107
Fasting value				
total lipids	+ 0.30**	+ 0.46**	− 0.07	+ 0.31**
chylomicrons	+ 0.30	+ 0.20	+ 0.11	+ 0.12
ß-lipoproteins	+ 0.28	+ 0.46**	− 0.03	+ 0.33
α-lipoproteins	− 0.13	+ 0.10	− 0.06	+ 0.10
Increase 3-hours after fat ingestion				
total lipids	+ 0.06	+ 0.27**	+ 0.01	+ 0.19
chylomicrons	− 0.00	+ 0.24	+ 0.11	+ 0.23
ß-lipoproteins	+ 0.05	+ 0.19	+ 0.01	+ 0.11
α-lipoproteins	+ 0.06	+ 0.14	+ 0.06	+ 0.09

however been demonstrated for patients with arterial hypertension.

RESULTS AND COMMENTS

PLASMA LIPIDS IN FASTING STATE

Several of the plasma lipids varied with the arterial blood pressure and particularly with the diastolic blood pressure, in both sexes (Tables 4 and 5). In the present investigation the males as well as the females were studied for any variation of the plasma lipids with age. In both males and females a correlation was found between age and total lipids ($r = +0.51^{**}$ and $+0.55^{**}$ respectively), chylomicrons ($r = +0.33$ and 0.26^{*} respectively) and β-lipoproteins ($r = +0.46$ and $+0.58^{*}$ respectively) but not for α lipoproteins. Those plasma lipids that varied significantly with the blood pressure thus increased with increasing age. Since the arterial blood pressure also increased with age it was thought that this co-variation might produce an apparent correlation between the plasma lipids and the blood pressure. The influence of age on the correlations were therefore eliminated, after which the correlations for the males were no longer significant. This indicates that the variation of the two factors with age were probably at least partly responsible for the correlation.

As for the females, the correlation coefficients were found to be numerically lower after elimination of the influence of age. The correlation between systolic blood pressure and the fasting value of the total lipids was, *however* still probably significant, and that between the diastolic blood pressure and the fasting value of the total lipids was significant. The β lipoproteins showed largely the same variation pattern with the blood pressure as did the total lipids. No correlation could be demonstrated between the blood pressure and chylomicrons or the α lipoproteins. This suggests that the β-lipoprotein fraction was the one responsible for the correlation in both cases. This assumption was also supported by the fact that no significant correlation was demonstrable ($r = -0.00$ and $+0.08$ respectively) after elimination of the influence of the β-lipoproteins on the partial correlations between the fasting value of the total lipids and the systolic and diastolic

Table 4. *Correlation between the systolic blood pressure and plasma lipids in fasting state and after fat ingestion, calculated partly as total correlation and partly as partial correlation independent of age.*

Plasma lipids	Systolic blood pressure			
	total correlation		partial correlation independent of age	
	males n = 85	females n = 107	males n = 85	females n = 107
Fasting value				
total lipids	+0.19	+0.43	−0.08	+0.22
chylomicrons	+0.29	+0.16	+0.16	+0.04
β-lipoproteins	+0.13	+0.46	−0.17	+0.21
α-lipoproteins	−0.06	+0.01	−0.02	+0.01
Increase 3-hours after fat ingestion				
total lipids	+0.05	+0.14	+0.02	+0.02
chylomicrons	−0.07	+0.06	−0.08	+0.03
β-lipoproteins	+0.09	+0.12	+0.07	−0.01
α-lipoproteins	−0.04	+0.21	−0.06	+0.18

blood pressure, respectively independent of age.

The regression of the systolic and diastolic blood pressure respectively on the fasting value of the ß-lipoproteins in females was studied (Figs. 12 and 13). The empirical regression lines for the systolic and the diastolic blood pressure respectively on the ß-lipoproteins fitted the theoretical regression line for the respective correlation well. In the scatter diagrams for the correlation between the systolic blood pressure and the diastolic blood pressure, respectively and the ß-lipoproteins the values crowded around the respective regression lines, and no extreme variants unduly influencing the respective correlation and regression coefficient could be seen.

In addition, it was tested whether the correlation between the ß-lipoproteins and blood pressure in the females could be ascribed to the co-variation of any of these variables with the fat factor. It was found that the correlations between the systolic blood pressure and the ß-lipoproteins, independent of back fat and side fat, respectively were significant (= + 0.38 and + 0.3… respectively) and the correlations between the systolic blood pressure and ß-lipoproteins independent of back fat and age, were probably significant (r = + 0.21) and independent of side fat and age, respectively not significant (r = + 0.17). The correlation between the diastolic blood pressure and ß-lipoproteins was studied in the same way. After elimination of the influence of back fat the correlation was still significant (r = + 0.41) as well as after the elimination of side fat (= + 0.38). The influence of age on these partial correlations was also studied, and the partial correlation thereby obtained between the diastolic blood pressure and ß-lipoprotein independent of back fat and age, and of side fat and age, respectively also proved significant (r = + 0.31 and + 0.29 respectively).

The correlation between systolic blood pressure and ß-lipoproteins thus appears to be due in the main to the variation of these factors varying with age, and no influence of the fat factors could be demonstrated with certainty. The influence of age was numerically less for the correlation between the diastolic blood pressure and the ß-lipoproteins,

Table 5. Correlation between the diastolic blood pressure and plasma lipids in fasting state and after fat ingestion, calculated partly as total correlation and partly as partial correlation, independent of age

Plasma lipids	Diastolic blood pressure			
	total correlation		partial correlation independent of age	
	males n = 83	females n = 107	males n = 83	females n = 107
Fasting value				
total lipids	+ 0.30	+ 0.44**	− 0.07	+ 0.33
chylomicrons	+ 0.30**	+ 0.29	+ 0.11	+ 0.12
ß-lipoproteins	+ 0.28	+ 0.46	− 0.03	+ 0.33
α-lipoproteins	− 0.13	+ 0.19	− 0.06	+ 0.10
Increase 3-hours after fat ingestion				
total lipids	+ 0.06	+ 0.27	+ 0.01	+ 0.19
chylomicrons	− 0.00	+ 0.24	+ 0.11	+ 0.23*
ß-lipoproteins	+ 0.03	+ 0.19	+ 0.01	+ 0.11
α-lipoproteins	+ 0.06	+ 0.14	+ 0.06	+ 0.08

and no influence of the fat factor could be demonstrated

On comparison between the results obtained in the present investigation and those available in the literature and referred to above, it should be borne in mind that in the present investigation the plasma lipids were determined by the method of SWAHN while the other investigators except WARIS (1958) used other methods Moreover in the investigations published by other workers individuals with arterial hypertension were compared with persons with normal blood pressure while in the present investigation the material consisted of healthy individuals In view of these differences it was decided not to compare the results reported by other authors with those obtained in the present investigation regarding the correlation between the total lipids and the blood pressure, for it might give misleading results

Although essentially the same objections can be raised against the results of

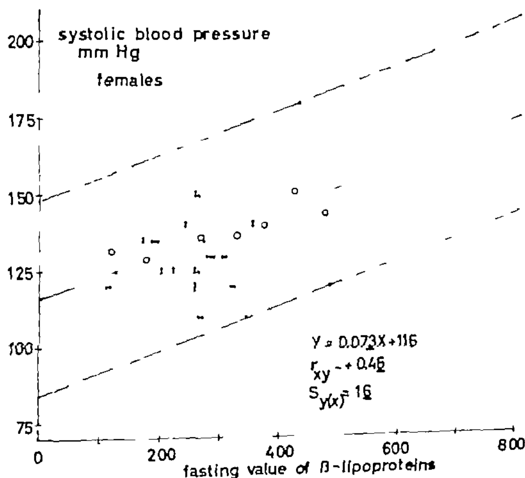


Fig. 12. Scatter diagram of correlation between systolic blood pressure (Y) and the fasting value of the ß-lipoproteins (X) in females. The continuous line denotes the theoretical regression line of the systolic blood pressure on the ß-lipoproteins. The interrupted lines denote the distance of twice the standard deviation from the regression line. The circles indicate the arithmetic mean of the systolic blood pressure in consecutive classes of ß-lipoproteins.

the β- and α-lipoproteins the results of the correlation analysis with these lipoprotein fractions and the blood pressure were compared with those given in the literature. The lack of any demonstrable correlation between the blood pressure and the β-lipoproteins in males is in agreement with the findings of LEWIS & PAGE (1953) and CORCORAN et al. (1957). The reservations mentioned above concerning the requirements for comparison may explain why the females in the present investigation showed a correlation between the β-lipoproteins and the blood pressure while no such correlation could be found in the last mentioned two investigations. As for the α-lipoproteins no correlation could be demonstrated with certainty with the blood pressure, and this is in

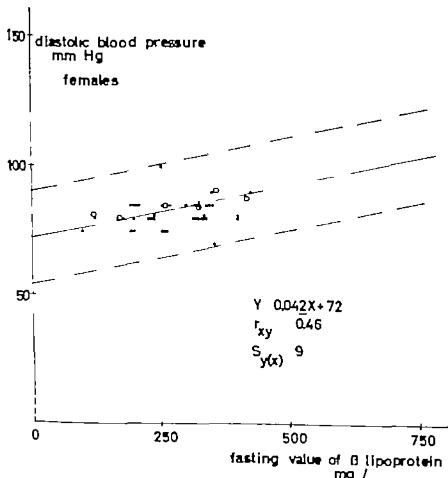


Fig. 13. *Scatter diagram of correlation between diastolic blood pressure (Y) and the fasting value of the β-lipoproteins (X) in females. The continuous line denotes the theoretic regression line of the diastolic blood pressure on the β-lipoproteins. The interrupted lines denote the distance of twice the standard deviation from the regression line. The circles indicate the arithmetic mean of the diastolic blood pressure in consecutive classes of β-lipoproteins.*

agreement with the findings previously published.

THE INCREASE OF PLASMA LIPIDS AFTER FAT INGESTION

In the investigation of the correlation between the blood pressure and the effect of fat ingestion on the plasma lipids the increase in the values found for the lipids 3 hours after ingestion of fat were used No significant correlation was found between this increase in the plasma lipids and the arterial blood pressure in the males (Tables 4 and 5)

As for the females a probably significant correlation was found between the systolic blood pressure and the increase of α lipoproteins but this weak correlation which was possibly due to chance, was no longer significant after elimination of the influence of age.

For the females a correlation was also found between the diastolic blood pressure and the increase of the total lipids and chylomicrons respectively But these correlations were not significant or probably significant respectively after the elimination of the effect of age

The maximal increase of total lipids in the plasma after fat ingestion showed no significant correlation with the systolic blood pressure in the males or females ($r = -0.01$ and $+0.15$ respectively) The diastolic blood pressure did not vary significantly with the maximal increase of the total lipids in the males ($r = +0.07$) but in the females the correlation was significant ($r = +0.25^*$) Since, in addition to the diastolic blood pressure the maximal increase of the total lipids increased with age in the females ($r = +0.22^*$), age might have influenced the correlation found This point was checked, and it was found that the correlation between the diastolic blood pressure and the maximal increase of the total lipids was no longer significant after elimination of the effect of age ($r = +0.19$)

No correlation could be demonstrated between blood pressure and increase of plasma lipids after fat ingestion, which is not in agreement with the results of BERKOWITZ (1961) This might be explained by the fact that the two materials are not quite comparable, since in the latter series individuals with arterial hypertension were compared with persons with a normal blood pressure and secondly different techniques were used for fat loading

DISCUSSION AND CONCLUSIONS

AGE

Statistics show that in general the average blood pressure rises with advancing years (Bruntön 1909, Symonds 1923, Gover 1948, Hamilton et al. 1954, Boe et al. 1956 and others). The present investigation showed the influence of the age not only on the arterial blood pressure but also on the correlations between blood pressure and different body variables. Several significant correlations found between the blood pressure and the factors studied disappeared after elimination of the influence of age on the co-variation, which indicates the absence of any direct causal relationship.

The cause of the rise in the blood pressure with advancing years has received much attention (Rusrek 1946). Some authors claim that the correlation is due to increasing circumference of the upper arm with age (Ragan & Bordley 1941, Wendkos & Rossman 1943, Boe et al. 1956, Bjerkedal 1957). No support for this theory was found in the present investigation, because elimination of the fat factor (arm fat) and of body weight, respectively, did not cause any change in the statistically demonstrated correlation between blood pressure and age.

The males in the 10—19 year age class had a fairly strong influence on some of the results. In this age class the age distribution was such that most males were still in the stage of development, while most of the females had passed this stage. The statistically significant difference found for the diastolic blood pressure between males and females in the entire series could be ascribed to impairment of the comparability of the sexes owing to differences in the age distribution of the males and the females, respectively, in this age class. This also applies to the correlation between the blood pressure and the muscle factor in the males, which was found to be due to the influence of the 10—19 year age class. The reason why the males in this age class were to such a great extent responsible for the correlation was partly because the average values found for the blood pressure and the muscle factors in this age class were low and partly because all of these values increased markedly during this period of life.

Age also had an effect on the correlation between blood pressure and body weight. Elimination of this influence reduced all the correlation coefficients numerically and abolished the significance of the correlation between the diastolic blood pressure and body weight found for the females.

BODY WEIGHT

In most investigations of the correlation between blood pressure and body weight, the latter has been corrected for body height, and then usually with the aid of standard weight tables (Symonds 1923, Faber 1924, Gover 1948, and Master et al. 1950). The influence of body height on the correlation between blood pressure and body weight was found to be small, which in view of the weakness of the correlation between

agreement with the findings previously published

THE INCREASE OF PLASMA LIPIDS AFTER FAT INGESTION

In the investigation of the correlation between the blood pressure and the effect of fat ingestion on the plasma lipids, the increase in the values found for the lipids 3 hours after ingestion of fat were used No significant correlation was found between this increase in the plasma lipids and the arterial blood pressure in the males (Tables 4 and 5)

As for the females, a probably significant correlation was found between the systolic blood pressure and the increase of α lipoproteins, but this weak correlation which was possibly due to chance was no longer significant after elimination of the influence of age

For the females a correlation was also found between the diastolic blood pressure and the increase of the total lipids and chylomicrons respectively But these correlations were not significant or probably significant, respectively after the elimination of the effect of age

The maximal increase of total lipids in the plasma after fat ingestion showed no significant correlation with the systolic blood pressure in the males or females ($r = -0.01$ and $+0.15$ respectively) The diastolic blood pressure did not vary significantly with the maximal increase of the total lipids in the males ($r = +0.07$) but in the females the correlation was significant ($r = +0.25$) Since, in addition to the diastolic blood pressure the maximal increase of the total lipids increased with age in the females ($r = +0.22$) age might have influenced the correlation found This point was checked, and it was found that the correlation between the diastolic blood pressure and the maximal increase of the total lipids was no longer significant after elimination of the effect of age ($r = +0.19$)

No correlation could be demonstrated between blood pressure and increase of plasma lipids after fat ingestion, which is not in agreement with the results of Berkowitz (1961) This might be explained by the fact that the two materials are not quite comparable, since in the latter series individuals with arterial hypertension were compared with persons with a normal blood pressure, and secondly different techniques were used for fat loading

tion. The strong influence of the in dividuals in the 10—19 year age class might be explained by the fact that they were still in a stage f development. During this stage there is a rapid growth inter ali of body dimensions not included in the present investigation, e g inner organ and body fluid, and these dimensions may be largely responsible for the correlation between the diast lic blood pressure and body weight

FAT FACTORS

Previous investigations in males have shown a correlation between the blood pressure and the fat fact rs, as measured by skinfold technique or direct tudies on the subcutaneous fat (LINDEGARD 19 7 WHYTE 1959 BJURULF 1959) In the present investigation the fat factors were found to vary significantly with the blood pressure in both sexes Fo the males the correlation was only apparent and due to the f ct that both the blood pressure and the fat factors increased with ge For the females this correlation was not due largely to age. The f t on the arm and on the thigh, respectively which in the present material did not increase with dvancing age, was also correlated with the blood pressure. Aft r elimination f the influence f ge on the relati nship the correlation coefficient was numerically higher f th systolic than for the diastolic blood pressure.

The bserv tion of RAGAN & BORDLEY (1941) that th apparent increase f the blood pressure as measured by th cuff method, increases with the thickness f the arm, could not be confirmed by the present in estigation. F t was found that the arm f t had n effect on the correlation between blood pressure and the f t n the side on the back. Of th fat factors the back and side fat ga the numerically trongest correla tions with the blood pressure. It has been hown th t hest fat (abov and t the right of th right nipple) and back fat (BROZEK & KEYS 1951) and side fat (PASCALE t al. 1956) ha e the closest correlation with the total body fat, measured by the gravimetric technique This might suggest that it was th t tal mount of body f t th t was responsible for the correlation between the blood pressure and the fat f ctors.

The individual blood pressure level appears to be dependent to no small extent on predisposing factors in the gene pattern f the individual. The blood pressure f twins deri ed from the same ovum was th s found to be strikingly equal, and it was concluded that the blood pres ure in health would seem to be largel n inherited constitutional characteristic (WEITZ 1926) MIALL & OLDHAM (1958) found a significant correlation between relati es and propo ut for both syst lic and diastolic blood pressure after elimination of the influence f the arm circumference and concluded that regarding the blood pressure there was a multifactorial inheritance to which familial environmental factors contribute a hare. It has also been hown that the correlation between th blood pressure and the subcutaneous f t is due to a co- ariation with the genetically determined f t cell numbe while no correlation could be demonstrated with the f t cell size, which ppears t be dependent mainly on environmental nutrition factors (BJU RULF 1959) Since neither arm f t nor thigh f t varied with age in the present material, it could not be excluded that the amount f f t in these two parts of the body were determined mainly genetically Though these fat fact rs howed only a weak correlation with th blood pressure in the females, n influence f age could be demonstrated. The correlations between th other fat factors and the blood pressure that persisted after elimination of the influence of age also suggest that the

blood pressure and body height was to be expected

Overweight, as judged with the aid of standard weight tables has often been ascribed mainly to increased body fat. The correlation between overweight and blood pressure has therefore usually been ascribed to increased amount of body fat As previously mentioned however differences in body weight between different individuals can also be due to differences in musculature skeleton inner organs and body fluid An advance in this direction was made by WHYTE (1959) in his analysis of the influence of age height, fatness and size of arm on the correlation between body weight and blood pressure in the males He found however that the partial correlation between body weight and blood pressure independent of these factors, was still probably significant

In the present investigation it was found that the correlation between body weight and systolic blood pressure in the females which was still significant after elimination of the influence of age, was due largely to the fat factors Concerning the males, no influence of the fat factor on the correlation between the systolic blood pressure and body weight was expected, because all the partial correlations between the systolic blood pressure and fat factors independent of age were not significant On the other hand, the correlation between handgrip length and sturdiness factors, respectively and blood pressure independent of age, persisted The influence of these factors was therefore eliminated This however produced no substantial change in the previously demonstrated significant correlations. Neither did it have any effect on the results when the calculations were made for the age classes 20—69 years only

Against the background of the results obtained it thus appears that the correlation between body weight and systolic blood pressure in females is due mainly to the fat factors, for nothing suggests that the other morphological body components studied were of any importance

As for the males, no effect of the fat factors could be demonstrated, which might, at least partly be explained by the distribution between the inner and outer fat The ratio between the inner and outer fat in females increases with advancing age (SKERLJ et al. 1953 and BROZEK 1956) Even if there does exist a high correlation between inner and outer fat the fat factor as determined by the skinfold technique, will successively underestimate the amount of inner fat with increasing age

Another possible cause of the correlation between body fat and the systolic blood pressure in males might also be discussed, namely variation in body fluid The treatment of different diseases with corticosteroids has taught that these hormones increase the blood pressure and the body weight The increase of body weight is due partly to the increase of the appetite with an increased amount of body fat as a consequence, and partly to an increased amount of body fluid. If an increased systolic blood pressure were associated with an increased amount of body fluid it would produce a correlation between the systolic blood pressure and body weight. The cause of the increase in body weight could not be ascribed to any of the body dimensions used in the present investigation Both the increased systolic blood pressure and the increased body weight might then be ascribable to an increased corticosteroid activity

The correlation found between the diastolic blood pressure and body weight of males was apparently due in the main to the individuals in the 10—19 year age class, and nothing suggested with certainty that any of the body variables studied was responsible for the correla

tion. The strong influence of the individuals in the 10—19 year age class might be explained by the fact that they were still in stage of development. During this stage there is a rapid growth inter alia of body dimensions not included in the present investigation, e.g. inner organs and body fluid, and these dimensions may be largely responsible for the correlation between the diastolic blood pressure and body weight.

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The observation of RAGAN & BORDLEY (1941) that the apparent increase of the blood pressure as measured by the cuff method, increases with the thickness of the arm, could not be confirmed by the present investigation. F it was found that the arm fat had no effect on the correlation between blood pressure and the fat on the side on the back. Of the fat factors, the back and side fat gave the numerically strongest correlations with the blood pressure. It has been shown that chest fat (also and to the right of the right nipple) and back fat (BROŽEK & KEYS 1951) and side fat (PASCALE et al. 1956) have the closest correlation with the total body fat, measured by the gravimetric technique. This might suggest that it was the total amount of body fat that was responsible for the correlation between the blood pressure and the fat factors.

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distribution of the series compared. The results obtained in the present investigation clearly showed how the influence of age can result in indirect correlation between the blood pressure and the plasma lipids. This i due to the fact that in the present material both th blood pressure and the t tal lipids, chylomicrons and ß-lipoproteins increased with increasing ge Thus, in males th correlation between the blood pressure and the plasma lipids in the fasting t t was not significant after elimination of the influence of age. In the females th influence of age tended to reduce th alues found for the correlation between the blood pressure and plasma lip ds, but for both the systolic, and particularly the diastolic blood pressure, the correlation with the total lipids and ß-lipoproteins persisted after elimination of the influence f age It was the ß-lipoproteins that were responsible for th correlation.

Both the blood pressure and the serum lipids occupy a central position in the discussion f the pathogenesis f atherosclerosis The correlation between the blood pressure and atherosclerosis need not be ascribed entirely to the mechanical effect f the blood pressure on the vessel walls f it might also be due to the blood pressure and atherosclerosis varying with other factors, such as the serum lipid The finding that the blood pressure in females aried with the ß-lipoproteins may thus serve as guide in the future investigation f certain aetiological factors of atherosclerosi Many authors hav tressed the correlation between atherosclerosis nd in creased cholesterol nd ß-lipoprotein respectively The common factor might be cholesterol, since the ß-l poprotein represent about two third of the serum cholesterol

In the females correlation was lso found between the diast lic blood pressure and the increase of the total lipid and chylomicrons 3 hours after the ingestion of f t, and the maximal increase f t tal lipids after fat ingestion, respectively Afte elimination of the influence of age the correlation between the diast li blood pres ure and chylomicrons was nly probably significant, but it hould be tressed that the other two correlations were almost statistically probably significant. The result thus only suggest the occurrence of a correlation between the diastolic blood pressure and the increase of the chylomicrons after fat ingestion Further investigations are desirable to elucidat this phenomenon.

SUMMING UP for males th results imply that the systolic blood pressure tended to increase with advancing age increa ing body weight and possibly also with increa ing skeletal length factors. N evidence was prod ced that the systolic blood pressure is influenced by the amount f subcutaneous fat, muscle factors or plasma lipids. The diastolic blood pressure tended to increase with age and body weight. The diast lic blood pres ure appeared to be independ ent f the amount of ubcutaneous fat, muscle factor keletal fact rs and plasma lipid

In the females the sy tolic blood pressure tended to increase with ge with body weight, with the amount of ubcutaneous fat and of ß-lipoproteins N influence of muscle or skeletal factors could be demon trated. The diastolic blood pres re tended to increase with advancing ge, with increasing amount f body fat, with decreasing keletal length facto with increasing ß-lipoprotein and possibly with increasing rise of the chylomicron after fat ingestion. No influence f the muscle factors could be demonstrated.

This means in other words that in men (Table 6) with a high body weight the blood pressure tend to be higher particularly with advancing ge, and possibly also the sy tolic blood pressure

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genetically determined part of the subcutaneous fat is responsible for the correlation with the blood pressure.

MUSCLE FACTORS

In a previous investigation no correlation has been found between blood pressure in males and muscle factors assessed by dynamometer recordings (LINDEGÅRD 1957) In the present investigation the muscle factors were significantly correlated with the blood pressure, independent of age, in the *males, but not in the females*. In the evaluation of the correlation between muscle factors and other factors the age distribution of a series must be considered During the age of development the muscle factor increases markedly From 20—29 years of age it tends to diminish

In the present material a difference in the stage of development was found between males and females in the age class 10—19 years Most of the males were still in the stage of development, while the females had largely passed this stage Elimination of the influence of age on the correlation between muscle factors and blood pressure for males did not prove to have any substantial effect on the correlation either It appeared, *however that the correlation between* the blood pressure and the muscle factors was ascribable mainly to the 10—19 years age class because the correlation lost its significance when the calculation was based on the age classes 20—69 years only

LENGTH AND STURDINESS FACTORS OF THE SKELETON

The sexes also varied regarding the correlations *between the length* and sturdiness factors, respectively of the skeleton and the blood pressure. Several significant correlations were found for the males, but none for the females. Age also proved to be largely responsible for the correlations found between the length and sturdiness factors, on one hand, and the diastolic blood pressure, on the other in the males The 10—19 year age class proved to be largely responsible *for the correlations found* between the systolic blood pressure and the length and sturdiness factors, respectively These correlations were no longer significant when calculated for the 20—69 year age classes only The weak correlations found after elimination of the influence of age on the last mentioned correlations allows no valid conclusions, even though all point in the same direction.

After elimination of the influence of age a correlation was found between the skeletal length factors and diastolic blood pressure in the females Thus a probably significant negative correlation was demonstrated between diastolic blood pressure on one hand, and radial length and tibial length, respectively on the other independent of age Various possible causal mechanisms of this correlation may be imagined. Since the *skeletal factors under discussion are* hardly influenced by environmental conditions, they may be regarded as environmentally stable factors (LINDEGÅRD 1956) If it be supposed that the correlation between skeletal length factors and the diastolic blood pressure in females indicates that these dimensions have a common determinant, it may thus be assumed that the correlation refers to an environmentally stable factor A possible *biological explanation* is that the correlation reflects the effect of genetic linkage.

PLASMA LIPIDS

In the evaluation of the correlation between blood pressure and plasma lipids the influence of age should also be *taken into account*. Some of the contradictory results in the literature can be ascribed to differences in the age

distribution of the series compared. The results obtained in the present investigation clearly showed how the influence of age can result in indirect correlation between the blood pressure and the plasma lipids. This is due to the fact that in the present material both the blood pressure and the total lipids, chylomicrons and β-lipoproteins increased with increasing age. Thus, in males the correlation between the blood pressure and the plasma lipids in the fasting state was not significant after elimination of the influence of age. In the females the influence of age tended to reduce the values found for the correlation between the blood pressure and plasma lipids but for both the systolic and particularly the diastolic blood pressure, the correlation with the total lipids and β-lipoproteins persisted after elimination of the influence of age. It was the β-lipoproteins that were responsible for the correlation.

Both the blood pressure and the serum lipids occupy a central position in the discussion of the pathogenesis of atherosclerosis. The correlation between the blood pressure and atherosclerosis need not be ascribed entirely to the mechanical effect of the blood pressure on the vessel walls, for it might also be due to the blood pressure and atherosclerosis varying with other factors, such as the serum lipids. The finding that the blood pressure in females varied with the β-lipoproteins may thus serve as a guide in the future investigation of certain aetiological factors of atherosclerosis. Many authors have stressed the correlation between atherosclerosis and increased cholesterol and β-lipoproteins, respectively. The common factor might be cholesterol, since the β-lipoproteins represent about two third of the serum cholesterol.

In the females a correlation was also found between the diastolic blood pressure and the increase of the total lipids and chylomicrons 3 hours after the ingestion of fat, and the maximal increase of total lipids after fat ingestion, respectively. After elimination of the influence of age the correlation between the diastolic blood pressure and chylomicrons was only probably significant, but it should be stressed that the other two correlations were almost statistically probably significant. The result thus only *suggests the occurrence of a correlation* between the diastolic blood pressure and the increase of the chylomicrons after fat ingestion. Further investigations are desirable to *elucidate this phenomenon.*

SUMMING UP for males the results imply that the systolic blood pressure tended to increase with advancing age, increasing body weight and possibly also with *increasing skeletal length factors.* No evidence was produced that the systolic blood pressure is influenced by the amount of subcutaneous fat, muscle factors or plasma lipids. The diastolic blood pressure tended to increase with age and body weight. The diastolic blood pressure appeared to be independent of the amount of subcutaneous fat, muscle factors, skeletal factors and plasma lipids.

In the females the systolic blood pressure tended to increase with age, with body weight, with the amount of subcutaneous fat and of β-lipoproteins. No influence of muscle or skeletal factors could be demonstrated. The diastolic blood pressure tended *to increase* with advancing age, with increasing amount of body fat, with decreasing skeletal length factor, with increasing β-lipoproteins and *possibly with increasing rise* of the chylomicrons after fat ingestion. No influence of the muscle factors could be demonstrated.

This means, in other words, that in men (Table 6) with a high body weight the blood pressure tends to be higher particularly with advancing age, and possibly also the systolic blood pressure

Table 6 *Correlation between systol c nd diastolic blood pressure, respectively and individu l characteristics for males and fem les corrected for age. + denotes positive correlation, (+) probable positi correlation — negative correlation and 0 no correlation*

Individual characteristics	Blood pressure			
	systolic		diastolic	
	males	females	males	females
age	+	+	+	+
body weight	+	+	+	0
subcutaneous fat	0	+	0	+
length fact	(+)	0	0	—
ß-lip fast value	0	+	0	+
chylom. increase	0	0	0	(+)

with increasing skeletal length factor and that women with a high body weight due to obesity show a tendency to have higher blood pressure, particularly with advancing age and increased ß lipoproteins and possibly an increased rise of the chylomicrons after fat ingestion In women with a small length factor the diastolic blood pressure tends to show a further increase

QUANTITATIVE STATISTICAL CORRELATIONS OF THE ARTERIAL BLOOD PRESSURE WITH AGE, SEX BODY BUILD FACTORS AND PLASMA LIPIDS IN FASTING STATE AND AFTER FAT INGESTION

The evaluation of the limit f the normal range f variation of the arterial blood pressure has often been based on the conception of normality f r a population, .e with reference to the frequency distribution of the blood pressure in the population.

The curve changes systematically with advancing age—the mean value increases d th range f variation becomes wider (WETHERBY 1932/33 HAMILTON et al. 1954 BOE et al. 1956. and others) This means that the level and range of variation of the normal blood pressure changes with ge. As shown in the present investigation, however in males and in f males the blood pressure varies not only with age but also with body build and in females also with the plasma lipids. This might serve as be is for further investigation f the normal range of variation f the blood pressure with due consideration to the influence of relevant factors on the blood pressure, as judged tatistically by multiple regression ana lyses. By inserting int the equations the values found f the respective dimensions in each ubject, it is possible to decide with a highe degree f certainty whether given blood pressure measured varies within n rmal limits

RESULTS AND COMMENTS

Since most of the males in the 10—19 year age class were in stage of development and thereby differed considerably from individuals in the other age classes the regression equations were based on data for males in the 20—69 year lasses only

The systolic blood pressure for males in the age classes 20—69 years varied with body weight and tibial length respecti ely aft r elimination of the influence of age It was also found that fat, m scle and keletal fact rs had no influence on the partial correlation between the systolic blood pressure and body weight, independent f age. Th correlation between systolic blood pressure and tibial length, independent of age, was so weak that no substantial influence on the regression equation of tibial length could be expected. W th this background a regression equation was calculated for males 20—68 years ld of the systolic blood pressure on age and body weight (Table 7).

The diastolic blood pressure fo males in the 20—69 year age classes varied with body weight after elimination of th influence of age. The correlations between th diastolic blood pressure and f t, muscle and keletal factors, respectively were not significant after elimination of the influence f age. The regression equation f th diastolic blood pressure on age and body weight was therefore calculated for males 20—68 years old (Table 7).

The syst lic blood pressure in the

T ble 7 *Equations of regression f systolic (SBP) and diastolic (DBP) blood pressure respectively in 73 males aged 20 to 68 years and 107 females aged 16 t 69 year on age (A) in different combinations n th body weight (W), skinfold thickness of side fat (F_S) and fasting valu of β-lipoproteins in plasma (L_β) R sidual standard deviation for the respective equation of regression is given. The t t l standard deviation in males wa 16.5 mm for SBP 6.9 mm for DBP and in females 17.9 nd 10_ mm., respectively*

Sex	V riables	Equations	Residual tandard deviation
Males 20–68 years n = 73	A	SBP = 118 + 0 371 A	15.3
	A+W	SBP = 80 + 0.367 A + 0 511 W	14 7
	A	DBP = 65 + 0 369 A	7 4
	A+W	DBP = 52 + 0 340 A + 0 185 W	7.2
Females 16–69 years n = 107	A	SBP = 117 + 0 529 A	15.6
	A+W	SBP = 88 + 0 428 A + 0.526 W	15 1
	A+F_S	SBP = 111 + 0.370 A + 1 11 F_S	14.5
	A+F_S+L_β	SBP = 107 + 0 271 A + 1 00 F_S + 0 029 L_β	14.2
	A	DBP = 75 + 0 233 A	9 4
	A+F_S	DBP = 72 + 0 183 A + 0 351 F_S	9.3
	A+F_S+L_β	DBP = 70 + 0 076 A + 0.239 F_S + 0 031 L_β	9 0

females varied with body weight fat factors and the plasma lipids in the fasting state, respectively after elimina tion of the influence of age The correla tion found between the systolic blood pressure and body height independent of age was ignored because it was presumably due to chance The correla tion between body weight and systolic blood pressure, independent of age appeared to be due mainly to fat factors and, because after elimination of the influence of back fat and side fat, respectively on the correlation, it was not significant and probably significant respectively Since visual evaluation suggested that the empirical regression line fitted th theoretical regression line of the sy blood pressure on side fat more mur ly than did the regression of the systolic blood pressure on back fat (Figs 5 and 7) it was decided to calculate the influence of side fat on systolic blood pressure The correlation between total lipids in the fasting state and systolic blood pressure, independent of age could be ascribed to the β-lipo-proteins since the correlation was no longer significant after elimination of the influence of the β-lipoproteins Against this background, and to facilitate the practical use of the regression equation it was decided to calculate them for the systolic blood pressure partly on age and body weight partly on age and side fat and partly on age side fat and β-lipo-proteins in the females (Table 7)

The diastolic blood pressure for females varied with fat factors skeletal factors plasma lipids in the fasting state and after fat ingestion respectively after elimination of the influence of age Of the fat factors back fat and side fat gave the numerically strongest correlation

with the diastolic blood pressure independent of age Since visual evaluation suggested that the empirical regression line fitted the theoretical regression line of the diastolic blood pressure on side fat more intimately than did the regression of the diastolic blood pressure on back fat (Figs. 6 and 8), it was decided t calculat the influence f side fat on diastolic blood pressure The skeletal factors were ignored because their correlation with the diastolic blood pressure, independent of age, were so weak that no substantial infl ence on the regression equation of skeletal fact rs could be expected. Fo the same reason the increase of chylomicrons after f t ingestion was not considered either The correlation between total lipids in the fasting stat and diastolic blood

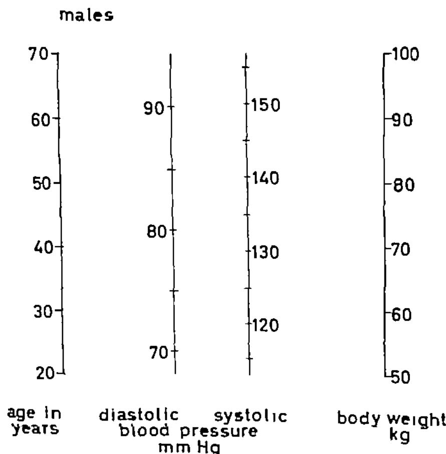


Fig 14. Nomogram of correlation in males, aged 20 to 68 years, between systolic and diastolic blood pressure, respectively on one hand, and age and body weight, on the other If line be drawn between the values for age and body weight on the scales for given individual, the line will cut the scales for systolic and diastolic blood pressure. The values at these points of intersection give the values for the systolic and diastolic blood pressure respectively corresponding to the values for age and body weight.

pressure, independent of age, could be ascribed to β lipoproteins, because this correlation was no longer significant after elimination of the influence of the β-lipoproteins To facilitate the practical application of the regression equations it was decided to calculate them for females of diastolic blood pressure on age and side fat, as well as on age, side fat and β-lipoproteins in the fasting state (Table 7)

When the limits of the normal blood pressure were calculated on the basis of a distribution curve the range was fairly wide. In the present investigation the arithmetic mean ± the standard deviation of the systolic blood pressure was 135 ± 16.5 mm Hg in the males,

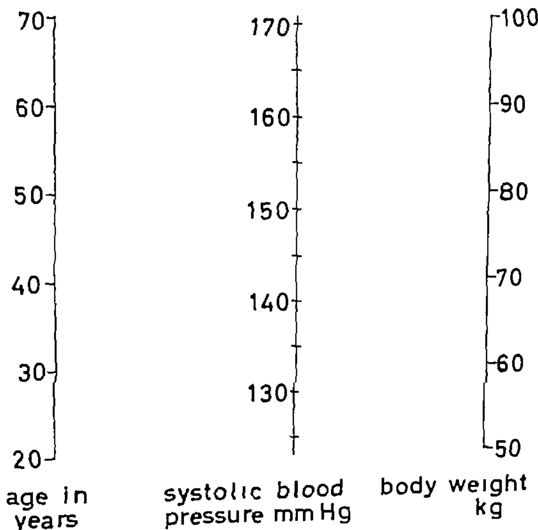


Fig. 15 Nomogram of correlation i females aged 16 to 69 years, between systolic blood pressur on one hand, and age and body weight, on th other If line be drawn between the values for age and body weight on th scales for given individual th lin will cut th scale for systolic blood pressure The value at this point of intersection gives th valu for th systoli blood pressur corresponding to th values for age and body eight.

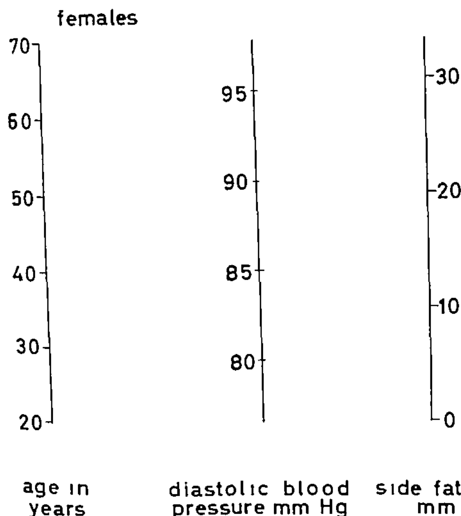


Fig. 16. *Nomogram of correlation in females aged 16 to 69 years, between diastolic blood pressure, on one hand, and age and skinfold thickness of the side fat, on the other. If line be drawn between the values for age and side fat on the scales for given individual the line will cut the scale for the diastolic blood pressure. The value at this point of intersection gives the value for the diastolic blood pressure corresponding to the values for age and side fat.*

aged 20 to 68 years and 136 ± 17 9 mm Hg in the females, aged 16 to 69 years The corresponding values for the diastolic blood pressure were 81 ± 8 9 mm Hg and 84 ± 10.2 mm Hg In the regression equations (Table 7) allowance is made for the influence of different factors on the blood pressure This enables a clearer opinion of what should be regarded as the normal blood pressure and its normal range of variation in a given person The normal standard deviation (see above) and the residual standard deviation (Table 7) show that this procedure enabled a narrowing of the range of variation of what may be regarded as the normal blood pressure.

To facilitate the practical medical application of the regression equations, some of them have been converted from mathematical to graphical form (Figs 14—16)

SUMMARY

The primary material consisted of 85 males, aged 11—68 years, and 107 females, aged 16—69 years. The 192 probands reported that they felt well. All of them were examined by the author. Unless otherwise stated, however, the results described below refer to 73 males, aged 20—68, and to 107 females, aged 16—69 years. The purpose of the investigation was to perform qualitative studies of the correlation between arterial blood pressure, on one hand, and age, sex, body build and plasma lipids in the fasting state and after fat ingestion, on the other hand, and to utilize the results obtained in a study of the quantitative statistical correlation between the blood pressure and the above-mentioned variables.

The resting blood pressure was measured with the subject lying and with a technique largely in accordance with the recommendations given by Ström & Werkö (1958) at the request of the Swedish Association of Cardiology and with those published jointly by the American Heart Association and the Cardiac Society of Great Britain and Ireland (1939). Body build was classified according to Lindegård's rating system (1953, 1956). The total plasma lipids and lipoproteins were determined by the method described by Swahn (1953).

The plasma lipids were studied partly in the fasting state and partly 2, 3, 4, 7 and 9½ hours after the intake of a test meal, containing 80—85 g milk fat.

The findings may be summarized as follows.

QUALITATIVE STATISTICAL CORRELATIONS IN MALES AND FEMALES OF BLOOD PRESSURE WITH AGE, BODY BUILD AND PLASMA LIPIDS

The systolic and the diastolic blood pressure increased with age in both sexes. In order to check whether this was due to an increase in the circumference of the upper arm with a consequent false, high blood pressure recording by the cuff method, the influence of the most important source of variation of the circumference of the upper arm with age, i.e. the subcutaneous fat on the arm, and, secondly the influence of body weight, on the correlation between blood pressure and age, were eliminated. These eliminations had no demonstrable effect on the correlation between the blood pressure and age.

A number of significant correlations could be demonstrated between the blood pressure and the body build variables studied. Many of these correlations, however, proved to be due to the influence of age (Tables 2—5). This suggests the absence of any causal correlation. Certain correlations were still significant after elimination of the influence of age.

It was also studied to what extent the most important morphological body components (fat, muscle, skeleton) was responsible for the correlations persisting between body weight and blood pressure after the elimination of the influence of age. In the males these variables had no demonstrable effect on the correlations

aged 20 to 68 years and 136 ± 17 9 mm Hg in the females aged 16 to 69 years The corresponding values for the diastolic blood pressure were 81 ± 8 9 mm. Hg and 84 ± 10.2 mm Hg In the regression equations (Table 7) allowance is made for the influence of different factors on the blood pressure. This enables a clearer opinion of what should be regarded as the normal blood pressure and its normal range of variation in a given person. The normal standard deviation (see above) and the residual standard deviation (Table 7) show that this procedure enabled a narrowing of the range of variation of what may be regarded as the normal blood pressure.

To facilitate the practical medical application of the regression equations, some of them have been converted from mathematical to graphical form (Figs. 14—16)

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found In the females, on the other hand body fat appeared to be of great importance since the significant correlation between body weight and systolic blood pressure, independent of age, became non-significant and probably significant after elimination of the influence of back *and side fat, respectively*

On analysis of the correlations between fat factors and blood pressure the results obtained differed with sex. In the males the correlations no longer persisted after elimination of the influence of age, while for females it remained significant *It was tentatively suggested that this* persistent correlation might be genetically linked The same biological causal mechanism was suggested for the demonstrated negative correlation between the skeletal length factor and the diastolic blood pressure in the females

No correlation could be demonstrated with certainty between the blood pressure and the muscle factors in the males or in the females

On continued analysis correlations were found between the blood pressure and some plasma lipids in both sexes After the elimination of the influence of age the correlations were no longer significant for the males For the females, on the other hand, probable significant correlations persisted between the total lipids and β lipoproteins respectively and the systolic blood pressure, and significant correlations between these 2 variables and the diastolic blood pressure No significant correlation was found between the blood pressure in males or females and the increase in the plasma lipids 3 hours after ingestion of a fatty meal.

QUANTITATIVE STATISTICAL CORRELATIONS IN MALES AND FEMALES OF THE BLOOD PRESSURE WITH AGE BODY BUILD AND *PLASMA LIPIDS*

A quantitative statistical analysis was made in males and females, of the blood pressure, on the basis of the results obtained in the qualitative studies of the correlation between blood pressure and the body variables measured. In this *study allowance was made for the* influence of the different body variables on the blood pressure

For the males a regression analysis was performed for the blood pressure in the age classes 20—69 years only and the regression equations of the systolic and the diastolic blood pressure, respectively on age and on age and body weight, respectively were calculated. For females the regression equations of *the systolic and diastolic blood pressure,* respectively were calculated on age, on age and side fat, and on age side fat and β lipoproteins in the fasting state, as well as of the systolic blood pressure on age and body weight (Table 7)

With the aid of the regression equations presented it is possible to form a more precise opinion of what should be regarded as the normal blood pressure and its normal range of variation in a *given person, as judged by* the conception of normality for a population i.e with reference to the frequency distribution of the blood pressure in the population. To facilitate the practical medical application of the regression equations some of them have been converted from mathematical to graphical form (Figs 14—16)

B. G.	18	64	7	11	12	26	14	18	34	31	9	162	242	341	85	120	70	497	109	257	131	−49	9	−48	−6	35
K. A.	18	53	3	6	5	6	10	16	36	37	24	167	240	367	84	110	78	318	32	179	101	97	63	33	1	113
K. S.	18	63	7	11	11	27	20	39	32	29	19	172	250	393	97	120	80	524	53	317	184	−63	17	−82	−28	76
S. S.	18	60	6	6	4	14	13	34	26	37	15	174	259	366	92	120	80	535	48	305	182	143	81	71	−9	143
E. O	18	66	11	16	14	25	21	37	36	41	23	167	254	374	90	140	90	569	85	348	136	211	89	138	14	211
B. J	18	65	9	21	17	23	23	35	31	42	25	161	225	345	87	120	85	486	115	255	116	149	79	59	11	149
G. B. O	18	47	5	7	4	9	11	12	30	39	22	153	227	337	81	125	75	537	102	253	182	19	12	22	−15	19
S. S.	18	62	7	11	6	31	18	22	34	27	17	170	236	341	83	135	85	517	104	271	142	77	21	44	12	77
M. G	18	56	6	11	6	15	16	21	32	33	25	162	236	360	82	130	95	481	70	306	105	128	70	59	−1	163
G. T	19	55	5	7	5	9	15	22	38	36	24	159	233	350	85	135	80	314	44	168	102	40	0	34	6	88
E. S.	19	62	9	18	15	23	18	27	32	32	18	173	256	400	90	140	80	379	66	241	72	60	−16	64	12	60
B. A.	19	69	8	8	7	20	20	37	27	38	21	164	250	370	88	125	75	387	63	221	104	87	59	23	5	87
B. Ö	19	51	8	5	5	11	16	24	33	34	18	164	249	368	81	130	85	329	43	178	108	101	65	58	−19	153
U N	19	52	6	7	5	9	13	29	31	45	23	149	209	318	81	125	75	310	50	161	99	118	62	27	29	118
L. H.	19	53	5	6	5	9	12	19	31	38	26	166	251	371	85	120	90	391	43	225	121	91	30	59	2	130
K. J	19	67	6	16	14	21	23	33	30	35	23	162	232	356	84	120	75	480	61	256	163	−4	32	−8	−28	33
K. B.	19	63	7	12	8	20	30	40	34	40	25	169	234	387	84	135	85	395	113	211	71	93	5	74	14	117

APPENDIX 1

SURVEY OF MATERIAL

Initials	Age (yr.)	Body weight (kg.)	Fat factors (thickness of skinfold in mm.)						Muscle factors (kp.)			Skeletal factors				Blood pressure (mm. Hg)		Fasting value (mg./100 ml.)				Increase after 3 hours (mg./100 ml.)				Max. increase Tot. lip
			Chin	Back	Side	Abd.	Arm	Thigh	Handgrip	Shoulder pull	Shoulder thrust	Body height (cm.)	Radial length (mm.)	Tibial length (mm.)	Fem. cond. breadth (mm.)	Syst.	Diast.	Tot. lip.	Chyl.	β-lip.	α-lip.	Tot. lip	Chyl.	β-lip.	α-lip.	
Males 10—19 years																										
C. A. E.	11	37	1	5	3	3	9	10	21	29	14	141	212	323	86	140	70	363	17	185	161	73	51	11	—19	87
T P	12	40	2	4	3	4	4	7	31	33	23	157	235	359	87	105	40	306	51	156	99	37	1	58	—22	98
P.-O. Å.	13	41	3	4	3	3	5	7	30	31	18	146	226	338	87	105	55	306	20	173	113	61	11	13	37	104
S.-G. G	13	34	4	5	3	4	10	11	21	24	13	145	216	320	85	110	65	365	39	263	63	65	13	53	—1	139
L. Å. L.	14	39	4	4	3	3	9	8	27	34	23	138	239	381	87	95	55	435	46	283	106	8	3	11	—6	57
Å. L.	14	60	4	4	4	8	7	8	31	46	18	176	283	422	95	120	50	522	66	339	117	25	109	—13	—71	25
R. C.	15	58	1	6	4	5	4	9	38	58	32	178	263	406	99	120	65	403	59	282	62	155	53	106	—4	266
L. G.	17	62	3	6	3	4	5	7	47	67	48	175	266	395	97	135	65	324	42	172	110	—25	24	—14	—35	34
H. M	17	77	3	3	3	3	6	7	49	56	43	189	286	422	104	130	85	307	73	218	16	67	2	42	23	70
J P	18	68	2	5	3	4	5	9	39	53	41	176	259	398	97	125	70	306	43	181	82	9	32	—10	—13	91
L.-G. L.	18	69	2	6	4	4	6	13	55	71	46	178	260	406	98	130	85	277	42	111	91	—1	—24	45	—22	29
J M	18	62	3	7	3	5	6	7	45	63	29	183	264	406	91	120	65	394	49	221	124	—11	38	—38	—11	87
Females 10—19 years																										
A. N	16	52	7	9	9	15	10	21	34	43	17	163	240	336	90	125	85	424	66	220	138	—26	—6	—27	—25	—26
I K.	17	59	3	7	6	13	10	16	31	38	24	166	242	365	85	120	75	297	93	115	89	—15	—3	2	—14	92
A. M. W	17	64	12	13	11	20	23	31	27	34	20	165	235	370	83	135	85	312	55	171	116	57	23	12	2	80
K. P	17	51	5	7	5	15	10	32	31	36	20	162	246	360	84	115	80	415	69	230	116	42	68	—11	—15	68
B O	18	59	8	14	13	28	13	30	30	29	17	161	[illegible]	330	90	135	80	568	63	341	164	127	83	48	—4	227

K. M.	29	57	7	7	6	9	13	21	29	42	25	170	217	341	89	125	85	214	43	133	68	67	50	3	14	86
E. L.	29	76	11	21	12	18	70	80	38	42	30	178	261	109	90	135	73	307	54	141	112	−33	16	−26	−23	38
M. V.	20	51	8	10	6	17	12	13	35	37	70	159	228	339	82	110	73	415	69	265	111	119	33	65	21	201
A. H.	21	55	5	5	4	12	11	29	33	30	19	167	239	362	84	125	75	283	67	99	117	101	50	20	31	190
G. B.	22	61	5	7	4	13	13	14	40	48	29	171	262	370	87	170	80	332	43	201	88	62	48	22	−8	71
O. L.	21	57	7	6	5	16	11	14	38	38	25	167	253	341	89	115	60	397	93	177	127	−9	−23	42	−20	−9
M. N.	21	53	5	8	5	16	9	18	23	27	13	148	206	311	81	120	80	258	88	112	58	185	116	61	8	333
A. P.	21	63	7	5	4	8	8	18	33	39	17	163	246	359	86	120	78	281	49	119	86	61	40	45	−24	72
I. P.	21	65	6	9	4	10	8	28	36	36	70	167	236	365	85	140	90	390	32	261	105	39	36	8	−5	47
G. V.	22	58	4	8	5	8	9	19	33	33	40	163	241	[illegible]	81	135	75	323	74	152	97	0	18	−11	−7	12
K. L.	22	51	6	8	8	12	12	34	28	36	19	151	204	303	87	153	115	523	[illegible]	275	120	235	141	100	−6	235
G. D.	22	47	9	9	7	16	10	17	33	34	23	156	223	319	87	130	70	551	41	353	157	111	56	56	2	111
B. H.	23	63	10	16	13	[illegible]	24	12	31	35	21	162	216	356	90	125	85	491	58	126	110	16	31	7	−25	27
E. O.	24	58	11	16	15	20	14	12	35	33	20	164	257	379	86	110	80	398	62	239	97	110	10	81	−11	122
A. M.	26	57	3	5	4	10	7	15	30	33	18	161	243	311	87	140	70	235	19	101	88	61	41	12	11	61
K. N.	26	76	6	17	19	29	76	18	39	36	18	162	232	349	87	140	90	501	135	214	152	−4	−16	−12	21	19
E. J.	28	70	9	16	11	22	13	29	27	29	13	162	230	369	84	125	80	417	91	253	68	179	31	132	16	38

Initials	Age (yr)	Body weight (kg)	Fat factors (thickness of skinfold in mm.): Chin	Back	Side	Abd.	Arm	Thigh	Muscle factors (kp): Handgrip	Shoulder pull	Shoulder thrust	Skeletal factors: Body height (cm.)	Radial length (mm.)	Tibial length (mm.)	Fem. cond. breadth (mm.)	Blood pressure (mm. Hg): Syst.	Diast.	Fasting value (mg /100 ml.): Tot. lip	Chyl.	β-lip.	α lip.	Increase after 3 hours (mg./100 ml.): T. t. lip.	Chyl.	β-lip.	α lip.	Max. increase Tot. lip.
Males 20—29 years																										
B. G	22	63	4	7	4	6	4	4	47	54	33	171	254	367	93	125	70	483	83	319	81	139	157	−27	9	139
O. H.	22	75	5	11	7	21	13	20	45	53	40	182	274	414	92	135	75	411	58	265	88	77	54	28	−5	89
L. P	22	70	5	9	9	11	9	14	53	59	27	175	270	409	101	100	60	400	76	266	58	72	−9	67	14	101
H. H.	23	51	5	5	4	9	4	4	42	35	25	171	247	376	88	125	75	405	48	207	150	87	50	29	8	93
L. L.	24	68	6	8	5	8	6	13	49	47	33	172	248	361	87	120	75	382	77	187	118	78	54	18	6	144
S. G	25	1	4	5	3	4	4	5	58	67	66	185	284	409	102	140	70	324	70	162	92	136	50	63	23	136
T. M	26	72	5	8	5	11	5	5	45	56	20	185	280	428	101	125	65	345	71	166	108	136	62	60	14	136
R. T	27	70	4	11	16	13	11	11	53	47	28	175	262	394	91	125	80	501	123	291	87	90	−8	58	40	90
B. L.	27	85	4	7	5	11	5	10	56	72	47	193	287	421	101	125	75	293	64	155	74	24	7	18	−1	60
G. W	27	56	4	6	4	4	5	6	51	65	59	173	270	400	97	125	80	522	92	289	141	99	60	50	−11	99
H. H	28	70	4	10	4	11	9	11	59	74	40	168	249	363	94	135	80	469	78	307	84	77	31	37	6	77
B. P	29	85	10	17	8	30	22	22	47	53	22	175	257	378	99	130	75	465	53	291	121	50	27	34	−11	119
Females 20—29 years																										
B. N	20	65	6	7	4	18	14	30	25	34	23	172	256	384	87	125	65	345	74	180	91	57	47	9	1	88
H. H	20	54	5	8	5	13	17	23	27	26	12	173	258	385	84	135	80	265	51	125	89	113	−6	93	26	113
I. P	20	58	8	8	6	10	16	24	35	40	23	162	251	372	85	135	80	321	6	183	88	58	56	1	1	63
B. G	20	56	5	8	5	20	12	16	31	32	19	164	244	356	86	135	80	293	49	143	101	−4	21	−8	−17	31
E. C.	20	60	10	14	21	34	28	33	37	40	19	167	271	384	86	130	80	412	47	283	82	17	52	−47	12	1

G. S.	33	53	8	11	6	21	27	13	33	30	17	160	245	366	85	125	75	344	71	191	103	33	33	−1	1	33
I. A.	33	53	7	12	9	20	8	24	38	39	23	162	229	311	83	120	85	714	111	428	175	202	109	108	−13	204
H. L.	31	69	10	12	6	18	18	31	33	36	19	171	271	375	93	125	85	439	104	172	162	55	14	43	−2	67
K. A.	33	50	4	9	4	13	14	12	29	29	9	161	232	361	80	120	80	196	101	232	139	90	31	25	31	149
C. M.	35	47	5	13	13	21	23	18	31	29	16	156	211	336	74	135	80	634	105	390	133	118	53	77	−12	162
T. B.	36	64	8	8	9	22	12	18	33	36	26	162	231	344	90	125	83	435	107	200	128	30	7	28	−8	91
A. M. Г	36	62	11	14	8	26	19	31	29	27	21	158	238	363	82	135	85	529	90	317	92	131	95	49	−13	131
B. F	36	53	6	8	6	14	20	21	38	31	16	163	235	369	83	135	75	504	86	317	175	−18	81	−29	−15	61
S. J	37	87	10	40	19	47	23	59	30	34	18	163	260	382	92	145	95	510	91	340	179	−19	−1	−39	21	48
H. H	38	60	4	5	3	6	9	11	33	37	21	173	261	391	90	125	80	159	42	257	160	19	16	−1	4	19
L. П	38	62	13	20	14	21	28	38	—	—	—	159	237	342	83	150	85	392	45	233	111	17	19	13	15	47
R. A.	38	61	7	12	18	21	11	27	32	34	16	160	225	332	86	145	105	576	78	288	210	10	34	−1	−22	11
A. M	39	58	8	9	10	17	15	18	32	32	19	162	251	351	87	115	80	491	41	359	88	199	101	96	2	199
L. F	39	54	5	7	4	11	11	16	36	33	16	163	246	368	86	125	75	442	82	199	161	−1	19	−2	−18	41

Initials	Age (yr.)	Body weight (kg.)	Fat factors (thickness of skinfold in mm.)						Muscle factors (kp)			Skeletal factors				Blood pressure (mm. Hg)		Fasting value (mg./100 ml.)				Increase after 3 hours (mg./100 ml.)				Max. increase Tot. lip
			Chin	Back	Side	Abd	Arm	Thigh	Handgrip	Shoulder pull	Shoulder thrust	Body height (cm.)	Radial length (mm.)	Tibial length (mm.)	Fem. cond. breadth (mm.)	Syst.	Diast.	Tot. lip	Chyl.	β-lip	α lip.	Tot. lip	Chyl.	β-lip	α-lip	
Males 30—39 years																										
B. H	30	84	4	9	7	17	10	9	53	61	35	189	285	444	102	160	80	586	112	-81	193	30	—10	45	—5	30
A. G	30	63	3	9	4	4	4	5	46	48	33	179	267	408	100	140	70	528	48	316	164	96	58	49	—11	96
H. H.	31	62	7	7	5	8	5	7	52	57	33	171	269	393	93	145	90	570	162	268	140	75	—17	81	11	98
G. H.	31	75	8	15	21	30	14	13	47	53	29	1 0	249	381	94	145	70	603	85	440	78	85	22	55	8	85
K. J	33	73	5	9	4	8	6	10	46	52	30	179	268	402	102	115	70	535	91	265	179	61	34	—3	30	61
A. S.	34	87	7	20	11	15	12	12	50	68	34	177	268	385	100	125	85	457	44	322	91	88	11	84	—7	176
S. N	36	65	4	7	9	14	10	8	47	45	29	174	262	382	92	120	85	576	95	358	123	16	6	21	—11	96
O. N	36	56	4	6	4	6	3	4	46	57	32	171	254	381	90	125	75	525	42	412	71	45	101	—39	—17	141
C. E. T	36	60	4	8	4	4	5	4	48	70	41	161	254	347	90	105	70	505	71	336	98	49	51	—4	2	120
E. F	37	71	6	10	13	18	9	17	55	59	34	183	268	393	92	125	85	639	118	361	160	88	100	—8	—1	131
H. S.	37	65	3	9	15	16	8	13	47	48	22	179	262	412	94	135	85	442	95	263	84	89	25	50	14	89
A. O	38	80	4	6	6	14	9	14	55	53	39	180	275	397	98	120	80	682	85	372	225	125	52	52	21	125
B. R.	38	75	5	13	14	16	8	6	53	65	43	182	272	422	101	140	85	581	108	444	29	246	124	114	8	318
Females 30—39 years																										
A. H	31	82	11	33	21	27	32	40	33	32	15	170	218	376	92	130	70	335	74	156	105	72	36	50	—14	146
K. D	32	61	11	20	13	29	16	11	31	29	16	167	245	371	86	120	70	339	44	171	121	76	27	36	13	6
L. P	32	80	12	25	21	31	31	54	41	46	28	166	251	352	96	133	85	287	28	135	121	82	35	42	5	82
L. L. P	32	59	7	8	6	14	12	18	37	29	11	172	214	381	87	110	70	427	30	275	122	69	77	18	—26	78
A. P	32	64	8	8	6	22	20	29	37	35	18	163	235	346	94	120	85	450	61	207	182	93	18	65	10	101

Females 40—49 years

I. L.	40	77	10	18	22	33	17	26	36	42	25	162	216	354	94	168	95	602	60	606	136	52	24	26	0	122
H. B.	40	51	5	8	6	9	11	16	37	40	28	161	250	363	80	165	105	590	51	389	138	122	57	69	−3	123
M. L.	40	60	8	9	6	14	17	22	27	41	19	162	232	364	93	138	85	400	64	191	142	14	−8	18	4	89
H. P	41	63	7	18	15	23	22	35	32	45	24	156	238	329	81	146	60	510	56	330	124	9	22	−1	−19	95
M. L.	41	55	7	13	7	13	16	26	23	37	18	171	235	376	80	116	78	415	78	288	102	89	14	64	9	89
B. H.	43	67	5	7	5	13	13	20	30	37	26	171	250	390	93	110	65	382	66	199	97	113	50	9	34	118
J. H.	43	53	5	6	4	10	6	13	34	33	17	164	243	365	84	150	85	534	101	321	112	67	37	10	20	170
G. F	44	59	13	11	14	27	15	35	34	35	24	159	229	356	82	145	90	517	114	258	145	90	14	43	34	151
E. R.	44	60	10	8	5	25	15	28	40	40	23	164	240	372	85	140	85	553	83	324	146	71	22	29	19	71
E. B.	47	60	14	13	14	29	18	29	29	31	14	166	213	361	90	160	90	530	101	283	146	113	60	71	−18	180
A. A.	47	71	11	22	33	33	23	37	36	46	23	138	225	318	90	180	90	735	140	423	172	159	62	86	11	159
M. S.	47	58	10	13	10	16	20	31	26	24	11	166	254	373	83	110	70	446	85	259	102	135	40	78	17	158
M.-O. R.	48	63	8	14	7	18	18	27	27	29	15	154	227	335	83	130	88	443	46	279	118	56	7	65	−16	56
L. L.	48	56	9	15	19	19	16	17	30	37	23	165	225	348	85	150	95	660	129	429	102	196	106	77	13	232
I. D.	49	60	11	16	10	28	14	18	33	28	20	168	252	377	86	125	80	574	67	327	180	65	55	−4	14	65

Initials	Age (yr.)	Body weight (kg.)	Fat factors (thickness of skinfold in mm.): Chin	Back	Skl	Abd.	Arm	Thigh	Muscle factors (kp.): Handgrip	Shoulder pull	Shoulder thrust	Skeletal f ctors: Body height (cm.)	Radial length (mm.)	Tibial length (mm.)	Fem. cond. breadth (mm.)	Blood l ressure (mm. Hg): Syst.	Diast.	Fasting value (mg./100 ml.): Tot. lip.	Chyl.	β-lip	α lip.	Increase after 3 hours (mg./100 ml.): Tot. lip	Chyl.	β-lip	α-lip.	Max. increase Tot. lip.
Males 40—49 years																										
S. A.	40	98	11	20	33	34	14	12	45	60	38	166	246	372	100	135	80	554	141	369	44	123	62	51	10	123
A. S.	40	73	5	10	11	14	11	9	42	58	38	179	281	402	96	125	75	531	88	353	90	—88	—12	—41	—35	7
A. A.	41	69	7	7	5	12	8	7	48	75	43	166	264	353	94	135	75	424	77	237	110	57	19	23	15	57
S. R.	42	69	3	7	4	8	5	5	48	65	43	177	259	384	97	110	75	504	45	368	91	47	19	28	0	94
G. L.	42	72	6	12	7	12	7	6	46	59	35	176	263	389	98	125	65	554	48	432	74	27	—1	27	1	47
L. H.	43	78	4	8	4	6	5	6	63	69	40	180	290	418	102	130	80	565	60	401	104	103	50	34	19	103
T P	44	72	6	8	10	11	5	5	54	52	40	170	253	377	90	150	90	528	109	303	116	28	16	—16	28	95
G. S.	45	85	6	14	6	21	7	10	53	71	40	176	260	381	100	120	80	541	90	346	105	—7	41	—31	—17	21
O O	47	55	5	7	6	9	4	6	48	56	31	170	266	395	90	120	70	700	84	497	119	133	20	91	22	133
F O	47	75	3	15	8	19	8	9	57	64	39	177	275	400	92	140	70	568	111	307	150	24	—19	48	—5	89
E. J	47	70	10	21	19	24	7	13	45	50	25	175	256	386	98	115	80	484	88	316	80	123	34	63	26	123
S. P	47	68	6	9	6	10	7	10	40	59	24	167	243	355	96	135	80	666	103	490	73	12	22	—35	25	20
H. B.	48	74	11	15	10	21	9	10	46	48	31	167	248	367	89	130	85	735	96	532	107	—16	45	—90	29	176
H.-E. N	48	67	5	10	6	14	8	9	41	51	35	177	253	375	101	135	80	521	65	349	107	27	—5	54	—22	62
G O	49	78	7	11	8	8	8	12	55	41	31	169	252	364	105	150	80	623	87	467	68	40	26	13	1	81
V L.	49	69	4	6	9	5	7	7	47	64	33	175	259	392	98	135	90	705	96	444	165	1	31	—23	—7	120

Females 40—49 years

L. L.	40	77	10	38	22	33	17	25	36	42	25	162	244	354	94	165	95	802	60	606	136	82	26	26	9	122
H. R.	40	51	5	8	6	9	11	16	37	40	28	161	250	363	80	165	105	590	81	309	158	123	57	69	−3	123
M. L.	40	60	8	9	6	14	17	22	27	41	19	162	232	356	93	135	85	400	64	191	142	14	−8	18	4	89
H. P	41	63	7	15	15	28	22	35	33	45	24	156	233	329	81	145	80	510	66	330	121	9	22	−3	−10	95
M. L.	41	55	7	12	7	13	16	26	28	37	18	171	235	376	80	118	75	415	75	238	102	89	14	66	9	89
B. H.	43	67	5	7	5	13	13	20	30	37	26	171	250	390	93	110	65	385	86	199	97	113	50	9	34	116
J. H.	43	53	5	6	4	10	6	13	34	33	17	164	213	365	84	150	85	531	101	321	112	67	37	10	20	170
G. F	45	59	13	11	14	27	15	35	34	35	24	159	229	356	82	145	90	517	114	258	145	90	14	42	31	154
K. R.	45	60	10	8	5	25	15	28	40	40	23	164	210	372	85	140	85	553	83	324	146	71	23	29	19	71
E. B.	47	60	14	13	14	29	18	29	29	31	14	166	213	361	90	160	90	530	101	283	146	113	60	71	−18	180
A. A	47	71	11	32	33	33	23	37	36	46	23	155	225	318	90	180	90	735	140	423	172	159	62	86	11	159
M. S.	47	58	10	15	10	16	20	31	26	24	11	166	254	373	83	110	70	416	85	259	102	135	40	78	17	155
M.-O. R.	48	63	8	14	7	18	18	27	27	29	15	154	227	335	83	130	80	443	46	279	118	56	7	65	−16	56
L. I	48	56	9	18	19	19	16	17	30	37	23	165	225	348	85	150	95	660	129	429	102	196	106	77	13	233
J. D.	49	60	11	16	10	28	14	18	32	28	20	168	252	377	86	125	80	574	67	327	180	65	55	−4	11	65

Initials	Age (yr)	Body weight (kg)	Fat factors (thickness of skinfold in mm.): Chi	Back	Side	Abd.	Arm	Thigh	Muscle factors (kp): Handgrip	Shoulder pull	Shoulder thrust	Skeletal factors: Body height (cm.)	Radial length (mm.)	Tibial length (mm.)	Fem. cond. breadth (mm.)	Blood pressure (mm. Hg): Syst.	Diast.	Fasting value (mg./100 ml.): Tot. lip	Chyl.	β-lip.	α lip.	Increase after 3 hours (mg./100 ml.): Tot. lip	Chyl.	β-lip.	α-lip.	Max increase Tot. lip.
Males 50—59 years																										
A. L.	50	69	6	9	5		9	8	45	62	30	1 6	254	382	86	155	90	476	107	298	1	21	7	13	1	21
G S.	50	82	6	12	23	17	11	15	51	61	43	181	278	391	105	125	80	554	44	363	147	36	36	50	—50	174
H R.	50	75	9	18	17	22	16	14	41	60	43	174	254	376	93	120	80	432	61	246	125	—11	34	—10	—35	38
S. G	51	73	8	16	19	16	8	9	51	57	38	171	248	377	98	135	90	565	45	435	85	—41	2	—18	—25	70
N C.	51	85	8	14	6	18	8	10	47	69	45	192	277	423	102	170	110	390	67	245	78	43	46	—1	—2	173
T O	52	79	6	14	10	15	10	7	50	45	29	187	277	431	102	135	85	520	32	423	65	45	50	—10	5	52
C. S	53	65	4	7	4	5	4	6	51	67	28	176	271	393	94	125	80	618	204	309	105	184	77	84	23	184
L. N	53	71	3	7	7	7	4	4	49	39	29	175	270	401	91	130	75	538	81	347	110	32	39	1	—8	143
E. H H	54	77	9	13	21	39	12	17	51	49	49	165	264	357	90	125	75	614	77	418	119	54	67	—11	—2	54
E. J	54	67	6	5	4	8	4	4	42	53	35	178	261	385	96	130	90	444	69	273	102	50	43	38	—31	69
E. S.	54	83	10	13	16	31	10	8	50	55	46	179	265	402	95	150	95	563	54	447	62	109	50	27	37	109
N S.	54	101	10	16	17	20	11	8	57	51	41	177	264	389	97	145	90	482	126	284	72	38	2	51	—18	49
O E.	56	76	11	14	16	22	13	17	46	67	31	171	273	378	89	140	95	423	43	319	61	95	38	41	—4	126
F H. V	56	84	4	10	15	15	6	7	57	63	37	177	269	401	102	150	95	578	87	433	58	124	43	80	1	208
A. B.	58	77	6	12	8	8	8	6	48	67	56	173	275	394	100	130	80	641	132	426	83	9	12	15	—18	13
Females 50—59 yrs																										
S. S	50	62	11	19	19	29	15	13	36	31	14	151	224	333	87	155	100	597	45	427	125	245	94	159	—8	245
L. H.	50	50	10	14	11	26	23	24	26	15	10	156	230	347	84	110	85	593	101	350	142	172	41	101	30	172
A. E.	2	59	8	12	8	23	17	20	31	22	10	167	244	382	87	155	100	281	63	141	80	64	31	33	0	65

Ч. P	52	87	16	19	49	35	32	56	20	26	3	160	231	352	86	15	110	188	59	351	78	83	4	85	4	102
Г. G.	53	71	8	18	17	32	19	46	49	34	18	166	214	316	100	120	85	524	68	301	155	103	61	59	−8	103
Ч. Н	53	4	14	19	23	49	22	12	33	32	17	160	213	366	91	150	90	521	99	287	135	71	11	47	13	99
Н. Г	83	67	9	13	7	32	35	42	35	33	19	163	211	378	90	150	95	665	97	158	113	106	65	31	10	106
Ч. S.	53	62	8	19	16	37	40	28	—			153	220	329	83	120	88	503	109	222	72	145	17	100	28	145
А. Ч.	55	56	10	12	14	21	24	23	23	31	15	151	199	306	63	110	85	555	91	100	61	151	41	107	6	166
Н. S.	54	61	10	14	19	35	18	19	31	34	16	167	233	387	85	170	100	598	111	314	172	257	117	112	17	47
F. N	56	61	12	16	25	26	19	37				158	221	316	85	145	80	535	72	337	123	96	1	36	−11	112
Ч. M. Г	56	72	9	14	9	46	17	35	30	46	21	162	[illegible]	350	88	160	88	482	61	306	118	102	11	50	11	114
A. K.	57	100	10	43	21	41	31	34	46	47	15	165	262	386	91	175	100	611	84	378	179	341	71	186	81	311
П. D.	57	73	7	10	7	39	13	32	33	40	22	160	239	357	95	110	85	518	77	318	131	198	91	115	−8	205
Ч. K	59	55	9	9	1	24	16	26	31	41	18	162	233	384	88	145	85	711	11	503	176	31	35	10	−14	31

Initials	Age (yr.)	Body weight (kg.)	Fat factors (thickness of skinfold in mm.)						Muscle factors (kp.)			Skeletal factors				Blood pressure (mm. Hg)		Fasting value (mg./100 ml.)				Increase after 3 hours (mg./100 ml.)				Max. increase Tot. lip
			Chin	Back	Side	Abd.	Arm	Thigh	Handgrip	Shoulder pull	Shoulder thrust	Body height (cm.)	Radial length (mm.)	Tibial length (mm.)	Fem. cond. breadth (mm.)	Syst.	Diast.	Tot. lip.	Chyl.	β-lip.	α-lip.	Tot. lip	Chyl.	β-lip.	α-lip.	
Males 60–69 years																										
L. H.	60	88	6	14	11	21	12	11	40	53	36	179	268	398	100	170	95	461	55	286	120	159	57	129	−27	159
H. H.	60	77	23	25	17	20	9	8	38	53	28	175	271	397	96	135	80	558	145	338	73	52	2	4	4	53
E. J	60	80	7	17	12	9	7	6	42	55	28	181	271	426	96	135	80	570	100	390	80	146	79	36	31	179
F. H	61	78	7	11	18	18	9	6	48	68	48	167	255	361	101	140	80	528	101	324	103	161	47	100	14	161
N. B.	61	86	6	26	20	22	15	8	51	5	40	180	284	408	96	155	90	492	62	315	115	31	51	−10	−10	64
J. A.	61	70	6	15	14	13	7	7	47	56	32	167	241	357	95	130	85	558	90	365	103	34	16	20	−2	34
E. F	61	73	4	11	8	16	8	6	53	64	39	174	266	398	93	135	85	436	66	318	52	108	65	50	13	108
G. N	62	64	5	9	11	6	5	5	46	54	28	169	249	360	91	160	90	537	67	382	68	14	5	12	−3	29
O. H	62	58	5	7	5	8	5	5	42	59	44	168	249	364	89	115	80	530	90	348	92	80	23	49	8	80
N.-I. N	63	72	6	10	23	19	8	9	43	44	27	176	271	403	99	140	90	437	96	212	129	55	20	61	−26	94
N. N	63	84	11	14	12	23	8	13	49	50	26	172	260	374	98	130	80	471	102	266	103	126	44	78	4	126
G. A.	63	89	4	14	13	31	10	15	41	48	31	179	271	419	96	110	80	519	68	383	70	67	61	−3	9	76
A. A.	64	94	10	13	19	19	10	15	51	61	24	177	279	408	103	200	100	600	174	321	105	22	25	12	−15	60
R. J	64	64	5	7	7	15	5	4	45	53	21	169	244	376	93	120	85	529	69	402	58	106	17	97	−8	134
O. M.	65	65	8	6	6	22	4	6	44	60	33	178	265	417	102	140	80	506	79	314	113	101	12	68	21	101
J. J	66	78	8	7	5	16	5	6	39	51	31	178	273	393	100	165	93	478	70	322	86	133	31	103	−1	133
A. A	68	65	10	6	8	8	4	4	40	50	21	174	269	407	91	155	95	496	60	352	84	22	49	−20	−7	88

Females 60—80 years

B. S.	60	67	10	11	19	18	11	12	29	26	18	172	266	397	93	153	85	509	30	446	106	138	42	78	18	138
O. J	60	71	10	9	8	27	12	12	29	32	10	171	267	395	96	175	95	397	44	370	83	88	82	12	−6	164
L. J	61	62	6	13	13	38	28	40	29	38	23	156	231	342	89	130	85	593	125	527	143	106	78	107	1	186
A. R.	62	62	11	14	18	34	13	12	27	33	18	163	234	379	88	140	85	800	174	561	73	64	14	38	14	103
F T	63	66	13	13	15	41	19	32	27	35	14	166	245	372	69	125	75	537	60	354	123	90	6	132	−42	105
E. F	63	59	10	22	15	38	14	19	29	32	14	161	238	382	90	150	90	444	80	255	109	−56	33	−51	−5	154
A. A.	64	80	6	17	11	33	20	47	31	40	14	167	267	379	93	145	90	639	90	450	99	115	31	78	6	118
B. M.	64	73	9	23	11	48	25	46	26	34	12	165	241	365	81	130	80	625	104	412	109	131	36	95	0	131
H. O.	64	64	12	11	8	32	17	28	23	32	10	156	232	257	91	165	105	507	61	340	86	196	54	125	7	186
L W	65	76	7	11	17	32	12	16	27	43	22	171	371	402	92	148	80	567	88	394	85	91	70	24	−3	165
E. O	66	64	13	19	12	35	11	14	25	28	9	161	240	366	90	150	80	445	74	251	120	208	119	114	−25	208
M N	66	72	13	17	14	55	17	36	27	27	13	162	253	363	89	150	100	446	97	253	136	45	−13	26	31	58
A. N.	68	72	12	11	12	22	18	38	30	31	18	164	272	380	92	140	80	483	41	336	106	5	15	−4	−6	31
B. A.	69	64	7	14	11	17	14	19	23	24	13	152	220	320	84	190	120	939	99	761	79	−8	45	−49	−4	76

APPENDIX 2

STATISTICAL METHODS AND SYMBOLS

Let x_1 x_2, x_n *denote a sample* f *n* measurements made on *n* individuals and x_i denotes each f *these individual values.*

Arithmetic mean $= \bar{x}$

Standard deviation $= s = \sqrt{\frac{1}{n-1}\Sigma(x_i - \bar{x})^2}$

Standard error of mean $\epsilon(\bar{x}) = \frac{s}{\sqrt{n}}$

For brevity I denote the sum of squares $\Sigma(x_i - \bar{x})^2$ by S_{xx}, the sum of products $\Sigma(x_i - \bar{x})$ $(y - \bar{y})$ *by* S_{xy}, *etc.*

COMPARISON OF INDEPENDENT MEANS

Two means $\bar{x}$ and $\bar{y}$ based on n_1 and n_2 measurements on individuals belonging to two separate groups, were compared by means of the *t* test

$$t = \frac{x - y}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$ where *t* has $n_1 + n_2 - 2$ degrees of freedom.

The difference was regarded as significant ( ) when the probability of its occurence by chance was less than 1 per cent ($P < 0.01$) *If the probability for the difference to be d e to chance was between one and five per cent* ($0.05 > P > 0.01$) th difference was said to be probably significant ( ).

TOTAL CORRELATION

Let (x_i, y_i) be pairs of variables and suppose that y depends, n the average, linearly upo x_i. The coefficient of correlation i calculated with th aid of th *formula*

$$= \frac{\frac{S_{xy}}{n} - x\ y}{s\ \ s}$$

The significance *of the product-moment correlation was also tested by the t test.* When the probability f a correlationcoefficient differing from zero was more than 99 per cent, the correlation was considered significant ( ). If the probability was less than 99 per cent but greater than 95 per cent, the correlation was considered probable ( ).

Since the extreme variants exert a relatively strong influence on th value of the dispersion as well as on the values found for the correlation and regression coefficients, measures were taken t counteract this influence. When a conclusion f pparently considerable importance wa based on a single significant correlation or regression, the following procedure was pplied The regression distribution was studied in detail by *comparing the theoretical regression line with* the empirical and secondly after the values had been plotted in scatter diagram (Fig. 1) The purpose of the scatte diagram was lso t t dy the shape of the empirical regression area.

PARTIAL CORRELATION

The partial correlatio betwee a variable (x) and another (y) *indepent of third* ( ) was calculated according to the formula

$$_{xy(z)} = \frac{_{xy} - \ _{xz}\ _{yz}}{\sqrt{(1 - \ _{xz}) \ (1 - r_{yz}^2)}}$$

In this formula $_{xy(z)}$ denotes the coefficient of the partial correlation under consideration; $_{xy}$ th coefficient of total correlation between the variables x and y r_{xz}, that between and z, nd $_{yz}$ that between y and z.

In rder t calculat th *partial correlation* between tw variables (x nd y) independent of two ther variables (and), th *following* form la wa used

$$r_{(xy)} = \frac{r_{xy(x)} - r_{xu(x)} \quad r_{yu(\;)}}{\sqrt{(1 - r_{xu(x)}^2)\,(1 - r_{yu(x)}^2)}}$$

In this formula $r_{xy(u)}$ denotes the coefficient of the partial correlation under consideration; $r_{xy(v)}$ the coefficient of partial correlation between and y independent of u, $r_{xu(v)}$ that between and independent of v, $r_{yu(v)}$ that between y and independent of

The significance of the coefficient of partial correlation was tested by t-test. The degrees of significance are indicated by the same symbol as for the coefficients of total correlations.

SIMPLE REGRESSION

a. Let (x_i, y_i) be pairs of measurements and suppose that y depends, on the average, linearly on x_i. The fitted regression line has the equation

$$y = \quad + bx$$

here the constants may be computed from the formula

$$b = \frac{S_{xy}}{S_{xx}} \qquad = y \quad b$$

The residual standard deviation $s_{y(x)}$ of the y (i. e. the variation which cannot be „explained„ by the x_i) is determined from the expression

$$s_{y(x)} = \frac{1}{-2}\Sigma(y_i - \quad - bx_i)^2 = \frac{1}{-2}(S_{yy} - bS_{xy})$$

Approximately

$$s_{y(x)} = s_y\,(1 \quad r^2)$$

here is the coefficient of correlation.

When is large (> 30) approximate 95 per cent confidence limits for single value y may be obtained from the formula

$$+ bx + 2 \; s_{y(x)}$$

I order to calculat the significance of the difference between t coefficients of regression t-test was performed by the classical method and the following formula was used

$$t = \frac{(b_1 - b_2)^2}{\frac{s_y \;(1 \quad r^2)}{(n_1 - 2)} + \frac{(1 - \quad ^2)}{(n_2 \quad 2)}}$$

here b_1, b_2 are the coefficient of regression, coefficient of correlation, s_y and standard deviation for the variables belonging to b_1 and b_2, respectively

$F_y(\;)$ indicates residuals, i. e. the difference between the individual observation of the variable y and the corresponding mean on the regression line of y on $Fy(x)$ thus means the residual of y independent of (Lindegård 1953, see also Sarnäs 1959).

MULTIPLE REGRESSION

a. Let $(x_i, y \quad z_i)$ be groups of three measured variables, and suppose that depends, on the average linearly upon x_i and y. The fitted regression line has the equation

$$= \quad + b_1 \quad + b_2 y$$

where

$$= \quad - b_1 \qquad b_2 y$$

and b_1, b_2 can be determined from the system of equations

$$b_1 S_{xx} + b_2 S_{xy} = S_{xz}$$
$$b_1 S_{xy} + b_2 S_{yy} = S_{yz}$$

The residual standard deviation $s_{z(xy)}$ is given by

$$s_{z(xy)} = \frac{1}{-3}\Sigma(z_i - \quad - b_1 \quad - b_2 y)^2$$

which can also be written

$$s_{z(xy)} = \frac{1}{-3}\Sigma(S_{zz} - b \;\; S_{xz} \quad b_2 S_{yz})$$

Confidence limits may be determined as in simple regression

b. Let $(\;\; y \qquad)$ be groups of four measured variables, and suppose that depends, on the average, linearly upon y and The fitted regression line has the equation

$$= \quad + b_1 x + b_2 y + b_3 z$$

where

$$= \qquad b_1 \quad - b_2 y - b_3$$

and b_1, b_2, b_3 can be determined from the system of equations

$$b_1 S_{xx} + b_2 S_{xy} + b_3 S_{xz} = S_{xu}$$
$$b_1 S_{xy} + b_2 S_{yy} + b_3 S_{yz} = S_{yu}$$
$$b_1 S_{xz} + b_2 S_{yz} + b_3 S_{zz} = S_{zu}$$

The residual standard deviation $s_{u(xyz)}$ is given by

$$s_{u(xyz)} = \frac{1}{-4}\Sigma(S_{uu} - b_1 S_{xu} - b_2 S_{yu} - b_3 S_{zu})$$

Confidence limits may be determined as in simpl regression.

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